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Optimisation des thérapies de stimulation/modulation électrique dans le traitement des troubles vésico-sphinctériens neurogènes et non neurogènes.

Sous la direction du Pr Patrick VERMERSCH

Sous la co-direction du Pr Stefan DE WACHTER

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Titre Français

Optimisation des thérapies de stimulation/modulation électrique dans le traitement des troubles vésico-sphinctériens neurogènes et non neurogènes.

Nederlandse title

Optimalisatie van elektrische stimulatie/modulatietherapieën bij de behandeling van neurogene en niet-neurogene aandoeningen van de lagere urinewegen.

English Title

Optimization of electrical stimulation/modulation therapies in the management of neurogenic and non-neurogenic lower urinary tract dysfunction.

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RÉSUMÉ

Introduction

Même s'il implique l'alternance d'une phase de remplissage et d'une phase de vidange, le cycle mictionnel normal ne peut se résumer à un fonctionnement binaire, mais implique la prise en compte constante de multiples facteurs : le niveau de remplissage du réservoir vésical, la sécurité de l'environnement dans lequel nous vivons, le contexte émotionnel dans lequel nous évoluons et les contraintes sociales auxquelles nous sommes soumis.

Nous savons aujourd'hui qu'il existe des altérations et/ou des modifications de l'activité et de la connectivité cérébrale, ainsi que des changements dans la régulation du système nerveux autonome, dans certains types de dysfonctionnements vésico-sphinctériens - notamment dans le syndrome clinique d'hyperactivité vésicale ou de l'incontinence urinaire par urgenturie et dans certains types de troubles de la vidange vésicale.

Parmi les thérapies disponibles aujourd'hui, les thérapies de modulation/stimulation électrique (neurostimulation tibiale et neuromodulation sacrée) semblent capables de normaliser et/ou de modifier l'activité et la connectivité cérébrale, ainsi que l'équilibre du système nerveux autonome. Elles pourraient donc apporter une réponse, au moins partielle, à certaines des étiopathogénies sous-jacentes à ces dysfonctionnements vésico-sphinctériens.

Cependant, le déploiement et le positionnement de ces thérapies de modulation/stimulation électrique sont encore limités par une compréhension incomplète de leurs mécanismes d'action, une identification imparfaite des indications et des populations les plus susceptibles de bénéficier de ces thérapies, un manque de consensus sur le réglage du courant électrique délivré et un manque d'évaluation à moyen et à long terme.

Il semble donc possible d'optimiser les thérapies de stimulation/modulation électrique dans la prise en charge des troubles vésico-sphinctériens neurogènes et non neurogènes, en s'attachant particulièrement aux points suivants : 1- Identifier les indications et les populations les plus susceptibles d'en bénéficier ; 2- Préciser le(s) mécanisme(s) d'action aigu(s) et chronique(s), notamment au niveau du système nerveux central et du système

nerveux autonome ; 3- Préciser la stratégie de réglage - à l'instauration du traitement et en cas de perte d'efficacité ; 4- Améliorer le suivi des patients et favoriser l'observance du traitement.

Dans la présente thèse, nous nous proposons d'aborder ces objectifs en trois parties :

Partie I : Avant l'instauration du traitement, interroger l'indication
Partie II : A l'instauration du traitement, interroger les mécanismes d'action
Partie III : Après l'instauration du traitement, interroger le suivi

Partie I : Avant l'instauration du traitement, interroger l'indication

Interventions précoces pour prévenir les dysfonctionnements vésico-sphinctériens après une lésion aigüe de la moelle épinière : une revue systématique

Tout d'abord, nous nous sommes interrogés sur le rôle des thérapies de stimulation/modulation électrique en tant qu'approches préventives. En effet, ces thérapies ne sont actuellement utilisées que comme des traitements symptomatiques, et ne sont donc initiées qu'une fois les dysfonctionnements vésico-sphinctériens observés. Or, dans la situation du patient blessé médullaire, où les dysfonctionnements vésico-sphinctériens sont quasi-systématiques, en lien avec l'émergence d'un automatisme médullaire, une approche préventive pourrait probablement avoir sa place - pour retarder ou réduire l'intensité des dysfonctionnements vésico-sphinctériens. Les thérapies de stimulation/modulation électrique, parce qu'elles pourraient favoriser la plasticité neuronale, semblent répondre à ce défi.

Cette revue systématique, réalisée conformément aux recommandations PRISMA, visait à synthétiser la littérature scientifique disponible sur les interventions précoces destinées à prévenir les dysfonctionnements vésico-sphinctériens survenant après une lésion aiguë de la moelle épinière. La revue a identifié les articles publiés jusqu'en avril 2021 dans les bases de données PubMed, Embase, ScienceDirect et Scopus, en utilisant des termes concernant les interventions précoces pour prévenir les dysfonctionnements vésico-sphinctériens après une lésion de la moelle épinière. Les sélections des résumés et des textes intégraux ont été

effectuées par trois évaluateurs indépendants, tandis que deux évaluateurs ont procédé à l'extraction des données de manière indépendante. Un article était considéré comme pertinent pour cette revue de la littérature s'il évaluait : un modèle *in vivo* de lésion de la moelle épinière, incluant un groupe ayant une intervention précoce comparé à au moins un groupe témoin, et rapportant des données cliniques, urodynamiques, biologiques et/ou histologiques.

Parmi les 30 études incluses dans la synthèse finale, 9 portaient sur la neurotransmission, 2 sur la réponse inflammatoire, 10 sur la neurotrophicité, 9 sur la modulation électrique des nerfs et 1 sur l'entraînement neuroprothétique multi-systèmes. Au total, 29/30 études ont fait état d'une amélioration significative des paramètres urodynamiques, tant pour la phase de remplissage que pour la phase de vidange. Ces résultats étaient souvent associés à des modifications substantielles au niveau de la vessie et de la moelle épinière, y compris une régulation à la hausse ou à la baisse de l'expression de certains neuromédiateurs et de certains récepteurs, une prolifération neuronale ou un bourgeonnement axonal et une réduction de la réponse inflammatoire et de l'apoptose.

La présente étude soutient donc le concept d'interventions précoces, notamment par le biais des thérapies de stimulation/modulation électrique, pour prévenir les dysfonctionnements vésico-sphinctériens après une lésion aigüe de la moelle épinière.

Réponse à la neurostimulation tibiale et à la neuromodulation sacrée dans le syndrome clinique d'hyperactivité vésicale : y-a-t-il une corrélation ?

Nous nous sommes interrogés sur la relation, en termes d'efficacité, entre la neurostimulation tibiale transcutanée et la neuromodulation sacrée. En effet, ces deux thérapies de stimulation/modulation électrique peuvent potentiellement se succéder dans nos algorithmes thérapeutiques. Clarifier ce point pourrait nous permettre de mieux accompagner nos patients dans le processus de décision médicale partagée. Ces résultats pourraient également nous aider à mieux comprendre les mécanismes d'action de ces deux thérapies. En effet, pour certains, ces deux approches pourraient être considérées comme une seule et même thérapie, à la différence que l'une cible directement la racine sacrée, alors que l'autre agit à distance. Cependant, à ce jour, aucune donnée ne permet de confirmer ou d'infirmer cette hypothèse.

Pour évaluer la corrélation entre la réponse à la neurostimulation tibiale transcutanée et la réponse ultérieure à la neuromodulation sacrée dans le traitement de l'hyperactivité vésicale, tous les patients ayant reçu consécutivement une neurostimulation tibiale transcutanée suivie d'un test de neuromodulation sacrée entre janvier 2016 et juin 2022 pour traiter l'hyperactivité vésicale dans deux centres hospitaliers universitaires ont été inclus. La réponse à chaque thérapie a été évaluée, le succès clinique étant défini par une amélioration de 50 % ou plus d'un ou plusieurs symptômes urinaires gênants par rapport à l'état initial. Le critère d'évaluation principal était la relation statistique entre la réponse clinique à la neuromodulation tibiale transcutanée et la réponse clinique à la neuromodulation sacrée, évaluée par régression logistique. Les critères d'évaluation secondaires étaient la relation statistique entre la réponse clinique à la neuromodulation tibiale transcutanée et la réponse clinique à la neuromodulation sacrée après contrôle du sexe, de l'âge (< 57 ans vs > 57 ans), de la présence d'une maladie neurologique sous-jacente et de la présence d'une hyperactivité détrusorienne, en ajoutant le facteur et l'interaction au modèle de régression précédent.

Parmi les 92 patients inclus, 68 étaient des femmes (73,9 %) et l'âge médian était de 57,0 [41,0-69,0] ans. Le succès clinique était rapporté chez 22 patients (23,9 %) sous neuromodulation tibiale transcutanée et chez 66 patients (71,7 %) pendant la phase de test de neuromodulation sacrée. Il n'y avait pas de corrélation statistique entre la réponse clinique à la neurostimulation tibiale transcutanée et la réponse clinique à la neuromodulation sacrée dans l'ensemble de la population ($_{CI95\%}$[0,48 ; 4,47] - p=0,51). De même, il n'y avait pas de corrélation statistique lorsque l'on contrôlait l'âge <57yo ou ≥57yo, avec p=1,0 et p=0,69, respectivement. Aucune étude statistique n'a pu être réalisée pour les autres sous-populations en raison de la petite taille des échantillons.

Nous avons conclu que la réponse à la neurostimulation tibiale transcutanée ne permettait pas de prédire la réponse à la neuromodulation sacrée dans le traitement de l'hyperactivité vésicale ; et que la neuromodulation tibiale transcutanée et la neuromodulation sacrée devaient être considérées comme des thérapies distinctes dans le processus de décision médicale partagée.

Développement d'un outil prédictif pour l'implantation de la neuromodulation sacrée dans le traitement du trouble de la vidange vésicale - une étude du comité de neuro-urologie de l'association française d'urologie

Nous nous sommes interrogés sur la possibilité de développer des outils prédictifs, notamment dans le cadre du trouble de la vidange vésicale. Dans cette indication, le taux de succès de la neuromodulation sacrée est très variable, allant de 33% à 100% selon les études. Disposer de tels outils prédictifs pourrait nous permettre de mieux accompagner nos patients dans le processus de décision médicale partagée. Ces résultats pourraient également nous aider à mieux comprendre les mécanismes d'action de la neuromodulation sacrée comme traitement du trouble de la vidange vésicale.

Le présent travail a été conçu comme une étude rétrospective incluant tous les patients ayant eu un test de neuromodulation sacrée pour trouble de la vidange vésicale entre 2000 et 2021 dans 11 hôpitaux universitaires. Le critère de jugement principal était défini comme le taux d'implantation définitive. Les critères de jugement secondaires comprenaient les changements dans les paramètres de vidange de la vessie. Des analyses de régression logistique univariée et multivariée ont été réalisées et ont permis de déterminer le rapport de cotes pour l'implantation définitive de la neuromodulation sacrée afin d'élaborer un outil prédictif. La performance de la discrimination du modèle multivarié a été évaluée à l'aide de la statistique c et une validation interne a été réalisée à l'aide d'un rééchantillonnage de type « *bootstrap* ».

Sur les 357 patients inclus, 210 (58,8%) ont finalement été implantés. Après régression logistique multivariée, 4 facteurs prédictifs ont été mis en évidence, dont l'âge (≤52 ans ; OR=3,31 $_{CI95\%}$[1,79 ; 6,14]), le sexe (femme ; OR=2,62 $_{CI95\%}$[1,39 ; 4.92]), la pression de clôture urétrale maximale (≥70cmH_2O ; OR=2,36 $_{CI95\%}$[1,17 ; 4,74]) et l'absence de maladie neurologique sous-jacente affectant le motoneurone inférieur (OR =2,25 $_{CI95\%}$[1,07 ; 4,76]). En combinant ces facteurs, nous avons établi 16 profils de réponse avec des taux d'implantation définitifs distincts, allant de 8,7 % à 81,5 %. La validation interne a révélé une bonne valeur de discrimination (statistique c, 0,724; $_{CI95\%}$[0,660 ; 0,789]) avec un faible biais d'optimisme (0,013). Cela nous a permis de développer un outil prédictif (https://predictivetool.wixsite.com/void).

La présente étude a permis d'identifier 4 facteurs prédictifs, permettant de développer un outil prédictif pour l'implantation définitive de la neuromodulation sacrée chez les patients présentant un trouble de la vidange vésicale, qui pourrait aider dans le processus de décision médicale partagée. La validation externe de l'outil doit encore être réalisée.

Partie II : A l'instauration du traitement, interroger les mécanismes d'action

Réponse aiguë du système nerveux autonome à la stimulation directe des racines sacrées dans le contexte de dysfonctionnement vésico-sphinctérien : une nouvelle approche pour comprendre le mécanisme d'action de la neuromodulation sacrée

Nous nous sommes interrogés sur l'effet d'une stimulation aiguë de la racine sacrée sur l'équilibre du système nerveux autonome. En effet, l'équilibre du système nerveux autonome semble être modifié, voire altéré, chez les patients présentant un dysfonctionnement vésico-sphinctérien, notamment dans le cas d'une hyperactivité vésicale ou d'un trouble de la vidange vésicale. Cependant, l'étude des mécanismes d'action des thérapies proposées dans ces contextes pathologiques s'est rarement attachée à comprendre leur effet sur l'équilibre du système nerveux autonome.

Dans cette étude monocentrique rétrospective, les patients ayant eu un test de neuromodulation sacrée dans un contexte de syndrome d'hyperactivité vésicale, de trouble de la vidange vésicale ou de syndrome douloureux vésical chronique entre mars 2022 et juin 2023 ont été inclus. Un protocole de stimulation standardisé était appliqué pendant l'implantation de l'électrode ; chacun des quatre plots étant stimulé séquentiellement à l'amplitude requise pour obtenir une réponse motrice anale. Les stimulations étaient étiquetées StimA, StimB, StimC et StimD, dans l'ordre croissant de l'amplitude minimale requise pour obtenir une réponse motrice anale. Les paramètres de variabilité de la fréquence cardiaque étaient recueillis à l'aide du moniteur PhysioDoloris et calculés par les méthodes du domaine temporel (SDNN, RMSSD), du domaine fréquentiel (LF, HF) et graphique (ANI).
Cinquante patients ont été inclus, dont 35 femmes. Douze patients présentaient une maladie neurologique sous-jacente. L'efficacité clinique était atteinte chez 16/28 patients (57,1 %) ayant une hyperactivité vésicale et chez 10/21 patients (47,6 %) ayant un trouble de la vidange vésicale. La variabilité du SDNN augmentait de manière significative pendant les stimulations

StimA à StimC, tandis que le SDNN maximum n'augmentait de manière significative que pendant la stimulation StimA. La variabilité de l'ANI augmentait de manière significative au cours des quatre stimulations, tandis que l'ANI maximum n'augmentait de manière significative que pendant la StimA.

Nous avons ainsi conclu que la stimulation directe de la racine sacrée était responsable d'une augmentation significative de l'activité du système nerveux autonome et de l'activité relative du système nerveux para-sympathique, avec un effet plus important observé lorsque la stimulation était délivrée plus près de la racine sacrée. Ces résultats mettent en lumière les mécanismes potentiels qui sous-tendent la neuromodulation sacrée, en particulier en ce qui concerne le traitement de la dysrégulation du système nerveux autonome dans les dysfonctionnements vésico-sphinctériens.

Partie III : Après l'instauration du traitement, interroger le suivi

Vie réelle après l'implantation définitive d'une neuromodulation sacrée : taux, raisons et facteurs de risque d'interruption du suivi à moyen terme

Enfin, nous nous sommes interrogés sur les résultats après l'implantation définitive de la neuromodulation sacrée, en particulier en ce qui concerne le suivi. En effet, si l'efficacité et la tolérance de la neuromodulation sacrée ont déjà été largement étudiées, aucune étude ne s'est encore intéressée au suivi après l'implantation définitive du dispositif. Or, au vu des quelques données "en vie réelle" publiées, dont un taux élevé de perte d'efficacité - qui pourrait nécessiter une révision du dispositif, une modification des réglages et/ou l'ajout d'un traitement concomitant - il semble plus que jamais important de s'interroger sur le suivi des patients, afin de développer à terme des parcours de soins plus adaptés.

Dans cette étude rétrospective multicentrique, tous les patients ayant bénéficié d'une implantation définitive de neuromodulation sacrée pour traiter un dysfonctionnement vésico-sphinctérien entre 2014-2019 au sein de 6 centres hospitaliers situés dans la région des « Hauts-de-France » (France) ont été systématiquement convoqués au cours de l'année 2020 pour une (télé)consultation standardisée. Les patients était répartis en 3 profils distincts selon la régularité de leur suivi postopératoire à 5 ans : "Suivi régulier", "Suivi irrégulier" et "Perdus de vue". Le critère de jugement principal était l'évolution de la proportion annuelle des 3

profils de suivi au cours des 5 années suivant l'implantation définitive. Comme critères de jugement secondaires, nous avons décrit les raisons rapportées d'interruption du suivi et recherché les facteurs de risque associés à cette interruption.

Au total, 259 patients ont été inclus. Au moment de la collecte des données, après un suivi moyen de 28,4 (±19,8) mois, 139 patients (53,7 %) avaient un "suivi régulier", 54 (20,8 %) un "suivi irrégulier" et 66 (25,5 %) étaient "perdus de vue". La proportion de patients bénéficiant d'un "suivi régulier" diminuait d'année en année, ne représentant plus que 46,2 % des patients à cinq ans. 175 patients (67,6 %) ont bénéficié d'une (télé)consultation standardisée. En analyse multivariée, seule la "méconnaissance du protocole de suivi" était statistiquement associée à l'abandon du suivi (OR=5,16 ; $_{CI95\%}$[2,12 ; 13,57]). La proportion de patients suivis après l'implantation définitive d'une neuromodulation sacrée diminuait donc régulièrement au fil des années, souvent en raison d'un manque d'éducation thérapeutique.

Ces données laissent entrevoir la nécessité de construire des parcours de soins plus adaptés et plus efficients après implantation définitive d'une neuromodulation sacrée.

Conclusion

En conclusion, bien que ces données doivent encore être complétées par de futurs projets de recherche, elles devraient nous permettre à terme d'optimiser davantage les thérapies de modulation/stimulation électrique dans la prise en charge des dysfonctionnements vésico-sphinctériens neurogènes et non neurogènes.

SAMENVATTING

Inleiding

De normale cyclus van de mictie kan niet worden herleid tot een binaire functie, maar houdt voortdurend rekening met meerdere factoren: de mate van blaasvulling, de veiligheid van de omgeving rondom on, de emotionele context waarin we ons ontwikkelen en de sociale beperkingen waaraan we onderhevig zijn.

We weten nu dat er bij bepaalde soorten blaassfincterdisfunctie - met name in het van overactieve blaassyndroom of urgentie-incontinentie, alsook bij bepaalde soorten blaasledigingsstoornissen veranderingen en/of modificaties zijn in de hersenactiviteit en connectiviteit, evenals veranderingen in de regeling van het autonome zenuwstelsel.

Van de huidig beschikbare therapieën, lijken elektrische modulatie/stimulatietherapieën (tibiale neurostimulatie en sacrale neuromodulatie) in staat om de hersenactiviteit en -connectiviteit te normaliseren en/of te wijzigen, alsook de balans van het autonome zenuwstelsel. Ze zouden daarom op zijn minst een gedeeltelijke oplossing kunnen bieden voor sommige onderliggende aandoeningen die voor blaas-sfincter disfuncties.

Het gebruik en de plaatsing van deze elektrische modulatie/stimulatietherapieën worden echter nog steeds beperkt door een onvolledige kennis van hun werkingsmechanismen, een onvoldoende identificaties van de juiste patientengroepen, een gebrek aan consensus over de gebruikte instellingen en een gebrek aan middellange en lange termijnsevaluatie.

Het lijkt daarom mogelijk om elektrische stimulatie/modulatietherapieën te optimaliseren bij de behandeling van patiënten met neurogene en niet-neurogene blaas- en darmstoornissen, met bijzondere aandacht voor de volgende punten: 1- Het identificeren van de indicaties en patiëntengroepen die er het meeste baat bij hebben; 2- Het specificeren van de acute en chronische werkingsmechanismen, met name in het centrale zenuwstelsel en het autonome zenuwstelsel; 3- Het specificeren van de aanpassingsstrategie van de stimulatieparameters-

bij aanvang van de behandeling en bij verlies van werkzaamheid; 4- Het verbeteren van de follow-up van patiënten en het stimuleren van therapietrouw.

In dit proefschrift stellen we voor om deze doelstellingen in drie delen te behandelen:

Deel I: Vóór het starten van de behandeling, het in twijfel trekken van de indicatie
Deel II: Bij het starten van de behandeling, de werkingsmechanismen onderzoeken
Deel III: Na het starten van de behandeling, kijken naar de follow-up

Deel I: Vóór het starten van de behandeling, de indicatie in twijfel trekken

Vroegtijdige interventies ter voorkoming van blaas- en darmfunctiestoornissen na acute dwarslaesie: een systematische review

Ten eerste hebben we de rol van elektrische stimulatie/modulatietherapieën als preventieve aanpak in twijfel getrokken. Deze therapieën worden op dit moment alleen gebruikt als symptomatische behandeling en worden daarom pas gestart als er een disfunctie van de blaas- en sluitspier wordt waargenomen. Echter, bij een dwarslaesiepatiënt, waar blaas-sfincterdisfuncties bijna systematisch zijn, gekoppeld aan het ontstaan van spinaal automatisme, zou een preventieve aanpak waarschijnlijk zijn plaats kunnen hebben - om de intensiteit van blaas-sfincterdisfuncties te vertragen of te verminderen. Elektrische stimulatie/modulatie therapieën, omdat ze neuronale plasticiteit zouden kunnen bevorderen, lijken aan deze uitdaging te kunnen voldoen.

Het doel van deze systematische review, uitgevoerd in overeenstemming met de PRISMA-aanbevelingen, was het samenvatten van de beschikbare wetenschappelijke literatuur over vroegtijdige interventies om blaas- en darmfunctiestoornissen na acute dwarslaesie te voorkomen. De review identificeerde artikelen die tot april 2021 waren gepubliceerd in de databases PubMed, Embase, ScienceDirect en Scopus met termen die betrekking hadden op vroegtijdige interventies om blaas-darm disfunctie na een dwarslaesie te voorkomen. Selecties van samenvattingen en volledige teksten werden uitgevoerd door drie

onafhankelijke beoordelaars, terwijl twee beoordelaars onafhankelijk van elkaar de gegevensextractie uitvoerden. Een artikel werd voor dit literatuuronderzoek relevant geacht als het een evaluatie bevatte van: een in vivo model van ruggenmergletsel, inclusief een vroege interventiegroep vergeleken met ten minste één controlegroep, en klinische, urodynamische, biologische en/of histologische gegevens rapporteerde.
Van de 30 studies die in de uiteindelijke synthese werden opgenomen, richtten 9 zich op neurotransmissie, 2 op ontstekingsreactie, 10 op neurotrofie, 9 op elektrische zenuwmodulatie en 1 op multisysteem zenuwprothese- training. In totaal rapporteerden 29/30 studies een significante verbetering in urodynamische parameters, zowel voor de vul- als de ledigingsfase. Deze resultaten werden vaak geassocieerd met substantiële veranderingen in de blaas en het ruggenmerg, waaronder up- of down-regulatie van de van bepaalde neurotransmitters en receptoren, expressies, neuronale proliferatie of axonale knopvorming, en verminderde ontstekingsreactie en apoptose.
De huidige studie ondersteunt daarom het concept van vroegtijdige interventies om blaas-sfincterdisfunctie na acute dwarslaesie te voorkomen, waardoor een potentiële preventieve aanpak in de komende decennia mogelijk wordt.

Antwoord op tibiale neurostimulatie en sacrale neuromodulatie bij klinisch overactief blaassyndroom: is er een correlatie?

We vroegen ons af wat de relatie in efficiëntie is, tussen transcutane tibiale neurostimulatie en sacrale neuromodulatie. In feite zouden deze twee elektrische stimulatie/modulatietherapieën elkaar kunnen opvolgen in onze therapeutische algoritmen. Als we hier meer duidelijkheid over krijgen, kunnen we onze patiënten beter ondersteunen in het medische besluitvormingsproces. Deze resultaten kunnen ons ook helpen om de werkingsmechanismen van deze twee therapieën beter te begrijpen. Voor sommigen zouden deze twee benaderingen inderdaad als één therapie kunnen worden beschouwd, met het verschil dat de ene direct gericht is op de sacrale wortel, terwijl de andere op afstand werkt. Tot op heden zijn er echter geen gegevens die deze hypothese bevestigen of weerleggen.

Om de correlatie te beoordelen tussen het klinisch antwoord op transcutane tibiale neurostimulatie en de daaropvolgende respons op sacrale neuromodulatie bij de behandeling

van OAB, werden alle patiënten geïncludeerd die tussen januari 2016 en juni 2022 opeenvolgend transcutane tibiale neurostimulatie en sacrale neuromodulatie kregen voor de behandeling van OAB in twee universitaire academische ziekenhuizen. Het therapeutisch effect werd beoordeeld, waarbij klinisch succes werd gedefinieerd als een verbetering van 50% of meer van een of meer hinderlijke plassymptomen ten opzichte van de uitgangswaarde. Het primaire eindpunt was de statistische relatie tussen het klinische antwoord op transcutane tibiale neuromodulatie en antwoord op sacrale neuromodulatie, beoordeeld met logistische regressie. De secundaire eindpunten waren de statistische relatie tussen het klinische antwoord op transcutane tibiale neuromodulatie en het klinische antwoord op sacrale neuromodulatie na controle voor geslacht, leeftijd (< 57 jaar vs > 57 jaar), de aanwezigheid van onderliggende neurologische aandoeningen en de aanwezigheid van detrusor overactiviteit, het toevoegen van factor en interactie aan het voorgaande regressiemodel.

Van de 92 geïncludeerde patiënten waren er 68 vrouw (73,9%) en de mediane leeftijd was 57,0 [41,0-69,0] jaar. Klinisch succes werd gemeld bij 22 patiënten (23,9%) onder transcutane tibiale neuromodulatie en bij 66 patiënten (71,7%) tijdens de testfase van sacrale neuromodulatie. Er was geen statistische correlatie tussen het klinische antwoord op transcutane tibiale neurostimulatie en dat op sacrale neuromodulatie in de totale populatie ($_{CI95\%}$[0,48; 4,47], p=0,51). Er was ook geen statistisch verband wanneer gecontroleerd werd voor leeftijd <57yo of ≥57yo, met respectievelijk p=1,0 en p=0,69. Er konden geen statistische studies worden uitgevoerd voor de andere subpopulaties vanwege de kleine steekproefomvang.

We concludeerden dat het antwoord op transcutane tibiale neurostimulatie de uitkomst van sacrale neuromodulatie bij de behandeling van OAB niet voorspelde; en dat transcutane tibiale neuromodulatie en sacrale neuromodulatie als afzonderlijke therapieën moeten worden beschouwd in het besluitvormingsproces.

Ontwikkeling van een voorspellend hulpmiddel voor de implantatie van sacrale neuromodulatie bij de behandeling van blaasledigingsstoornissen - een onderzoek door de neuro-urologiecommissie van de Franse urologievereniging.

We onderzochten de mogelijkheid om voorspellende instrumenten te ontwikkelen, met name in de context van blaasledigingsstoornissen. Bij deze indicatie is het succespercentage van sacrale neuromodulatie zeer variabel, variërend van 33% tot 100%, afhankelijk van het onderzoek. Als we over zulke voorspellende tools zouden beschikken, kunnen we onze patiënten beter ondersteunen in de medische besluitvorming. Deze resultaten kunnen ons ook helpen om de werkingsmechanismen van sacrale neuromodulatie als behandeling voor blaasledigingsstoornissen beter te begrijpen.

Dit werk was opgezet als een retrospectieve studie van alle patiënten die tussen 2000 en 2021 in 11 academische ziekenhuizen een sacrale neuromodulatietest ondergingen voor blaasontledigingsstoornissen. De primaire uitkomst was gedefinieerd als het aantal definitieve implantaties. Secundaire uitkomsten waren veranderingen in blaasledigingsparameters. Univariaat en multivariaat logistische regressieanalyses werden uitgevoerd om de odds ratio voor definitieve sacrale neuromodulatie-implantatie te bepalen om een voorspellend instrument te ontwikkelen. De discriminatieprestatie van het multivariate model werd beoordeeld met de c-statistiek en interne validatie werd uitgevoerd met bootstrap resampling.

Van de 357 geïncludeerde patiënten werden er uiteindelijk 210 (58,8%) geïmplanteerd. Na multivariaat logistische regressie werden 4 voorspellende factoren geïdentificeerd, waaronder leeftijd (≤52 jaar; OR =3,31 $_{CI95\%}$[1,79; 6,14]), geslacht (vrouw; OR=2,62 $_{CI95\%}$[1,39; 4.92]), maximale urethrale sluitdruk (≥70 cmH_2O; OR=2,36 $_{CI95\%}$[1,17; 4,74]) en afwezigheid van onderliggende neurologische aandoening van het lage motorneuron (OR =2,25 $_{CI95\%}$[1,07; 4,76]). Door deze factoren te combineren, stelden we 16 antwoordprofielen vast met verschillende definitieve implantatiepercentages, variërend van 8,7% tot 81,5%. Interne validatie toonde een goede discriminatiewaarde (c-statistiek, 0,724; $_{CI95\%}$[0,660 tot 0,789]) met een lage optimismebias (0,013). Dit stelde ons in staat om een voorspellende tool te ontwikkelen (https://predictivetool.wixsite.com/void).

De huidige studie identificeerde 4 voorspellende factoren, waardoor het mogelijk werd een voorspellende tool te ontwikkelen voor definitieve implantatie van sacrale neuromodulatie bij patiënten met blaasledigingsstoornissen, die zou kunnen helpen bij het medische besluitvormingsproces. Externe validatie van het instrument moet nog worden uitgevoerd.

Deel II: Aan het begin van de behandeling, de werkingsmechanismen in twijfel trekken

Acute antwoord van het autonome zenuwstelsel op directe stimulatie van de sacrale wortels in de context van blaas-sfincterdisfunctie: een nieuwe benadering om het werkingsmechanisme van sacrale neuromodulatie te begrijpen

We onderzochten het effect van acute stimulatie van de sacrale S3 wortel op het evenwicht van het autonome zenuwstelsel. De balans van het autonome zenuwstelsel lijkt te veranderen, of zelfs te veranderen, bij patiënten met blaassfincterdisfunctie, vooral in het geval van blaashyperactiviteit of blaasledigingsstoornissen. De studie van de werkingsmechanismen van therapieën die in deze pathologische context worden voorgesteld, heeft zich echter zelden gericht op het begrijpen van hun effect op de balans van het autonome zenuwstelsel.

In deze retrospectieve studie in één centrum werden patiënten geïncludeerd die tussen maart 2022 en juni 2023 een sacrale neuromodulatietest ondergingen in de context van een overactief blaassyndroom, blaasledigingsstoornis of chronisch bekkenpijnsyndroom. Tijdens de implantatie van de elektroden werd een gestandaardiseerd stimulatieprotocol toegepast, waarbij elk van de vier contactpunten opeenvolgend werd gestimuleerd met de amplitude die nodig is om een anale motorische respons op te wekken. Stimulaties werden StimA, StimB, StimC en StimD genoemd, in oplopende volgorde van de minimale amplitude die nodig is om een anale motorische respons op te wekken. Hartslagvariabiliteitsparameters werden verzameld met de PhysioDoloris-monitor en berekend met tijddomein- (SDNN, RMSSD), frequentiedomein- (LF, HF) en grafische (ANI) methoden.
Vijftig patiënten werden geïncludeerd, waarvan 35 vrouwen. Twaalf patiënten hadden een onderliggende neurologische aandoening. Klinische effect werd bereikt bij 16/28 patiënten (57,1%) met een overactieve blaas en bij 10/21 patiënten (47,6%) met een blaasontledigingsstoornis. Variabiliteit in SDNN nam significant toe tijdens StimA tot StimC stimulatie, terwijl maximale SDNN alleen significant toenam tijdens StimA stimulatie. ANI variabiliteit nam significant toe tijdens alle vier stimulaties, terwijl maximale ANI alleen significant toenam tijdens StimA.

We concludeerden dus dat directe stimulatie van de sacrale wortel verantwoordelijk was voor een significante toename in de activiteit van het autonome zenuwstelsel en de relatieve activiteit van het para-sympatische zenuwstelsel, waarbij een groter effect werd waargenomen wanneer stimulatie dichter bij de sacrale wortel werd toegediend. Deze resultaten benadrukken de potentiële mechanismen die ten grondslag liggen aan sacrale neuromodulatie, in het bijzonder met betrekking tot de behandeling van ontregeling van het autonome zenuwstelsel bij blaassfincterdisfunctie.

Deel III: Na de behandeling, follow-up vragen

Het echte leven na definitieve implantatie van sacrale neuromodulatie: percentages, redenen en risicofactoren voor stopzetting van middellangetermijnfollow-up

Tot slot vroegen we ons af wat de resultaten zijn na definitieve implantatie van sacrale neuromodulatie, met name wat betreft follow-up. Hoewel de werkzaamheid en tolerantie van sacrale neuromodulatie al uitgebreid zijn onderzocht, is er nog geen onderzoek gedaan naar de follow-up na definitieve implantatie van het apparaat. Met het oog op de weinige gepubliceerde "real-life" gegevens, waaronder een hoog percentage verlies van werkzaamheid - wat een revisie van het apparaat, een verandering van instellingen en/of de toevoeging van een bijkomende behandeling nodig zou kunnen maken - lijkt het echter belangrijker dan ooit om naar de follow-up van patiënten te kijken, om meer geschikte zorgpaden op de lange termijn te ontwikkelen.

In deze multicentrische retrospectieve studie werden alle patiënten die tussen 2014 en 2019 een definitieve sacrale neuromodulatie-implantatie ondergingen om blaassfincterdisfunctie te behandelen in 6 ziekenhuizen in de regio Hauts-de-France (Frankrijk), systematisch opgeroepen voor een gestandaardiseerde (tele)raadpleging in 2020. De patiënten werden verdeeld in 3 verschillende profielen op basis van de regelmaat van hun postoperatieve follow-up na 5 jaar: "Regelmatige follow-up", "Onregelmatige follow-up" en "Lost to follow-up". De primaire uitkomst was de verandering in de jaarlijkse proportie van de 3 follow-up profielen gedurende de 5 jaar na de definitieve implantatie. Als secundaire uitkomsten beschreven we de gerapporteerde redenen voor het stopzetten van de follow-up en

onderzochten we de risicofactoren die geassocieerd werden met het stopzetten van de follow-up.

In totaal werden 259 patiënten geïncludeerd. Op het moment van gegevensverzameling, na een gemiddelde follow-up van 28,4 (±19,8) maanden, hadden 139 patiënten (53,7%) een "regelmatige follow-up", 54 (20,8%) hadden een "onregelmatige follow-up" en 66 (25,5%) waren "lost to follow-up". Het aandeel patiënten met 'regelmatige follow-up' daalde van jaar tot jaar en vertegenwoordigde slechts 46,2% van de patiënten na vijf jaar. 175 patiënten (67,6%) kregen een gestandaardiseerd (tele)consult. In multivariate analyse was alleen "gebrek aan kennis van het follow-upprotocol" statistisch geassocieerd met het stopzetten van de follow-up (OR=5,16; $_{95\%CI}$[2,12-13,57]). Het percentage patiënten dat werd opgevolgd na definitieve implantatie van sacrale neuromodulatie daalde dus gestaag in de loop der jaren, vaak door een gebrek aan therapeutische educatie.

Deze gegevens suggereren de noodzaak om meer geschikte en efficiënte zorgpaden te ontwikkelen na definitieve implantatie van sacrale neuromodulatie.

Conclusie

Hoewel deze gegevens nog moeten worden aangevuld door toekomstige onderzoeksprojecten, moeten ze ons uiteindelijk in staat stellen om elektrische modulatie/stimulatietherapieën verder te optimaliseren bij de behandeling van neurogene en niet-neurogene blaas- en darmfunctiestoornissen

SUMMARY

Introduction

Even though it corresponds to the alternation between a bladder filling phase and a bladder emptying phase, the normal micturition cycle cannot be summed up as a binary operation but involves the constant consideration of multiple factors: the filling level of the bladder reservoir, the safety of the environment in which we live, the emotional context in which we evolve and the social constraints to which we are subjected.

We now know that there are alterations and/or modifications in brain activity and connectivity, as well as changes in the regulation of the autonomic nervous system (ANS), in certain types of lower urinary tract dysfunctions - notably in overactive bladder and urge urinary incontinence, and in certain types of voiding dysfunctions.

Among the therapies available today, electrical modulation/stimulation therapies (tibial neurostimulation and sacral neuromodulation) appear able to normalize and/or modify brain activity and connectivity, as well as the balance of ANS. They could thus provide at least a partial response to some of the etiopathogenies underlying these lower urinary tract dysfunctions.

However, the deployment and positioning of these electrical modulation/stimulation therapies are still limited by an incomplete understanding of their mechanisms of action, imperfect identification of the indications and populations most likely to benefit from these therapies, a lack of consensus on the setting of the electrical current delivered, and a lack of mid and long-term evaluation.

It therefore seems possible to optimize electrical stimulation/modulation therapies in the management of neurogenic and non-neurogenic lower urinary tract dysfunctions, focusing particularly on the following points : 1- Identifying the indications and populations most likely to benefit; 2- Clarifying acute and chronic mechanism(s) of action, particularly at the level of the central nervous system and autonomic nervous system; 3- Specifying setting strategy - at

initiation and in the event of loss of efficacy; 4- Improving patient follow-up and promoting treatment adherence.

In the present thesis, we propose to address some of these objectives in 3 parts:

Part I: Before therapy initiation, Questioning the indication
Part II: At therapy initiation, Questioning the mechanisms of action
Part III: After therapy initiation, Questioning the follow-up

Part I: Before therapy initiation, Questioning the indication

Early interventions to prevent lower urinary tract dysfunctions after spinal cord injury: a systematic review

To begin with, we questioned the role of electrical stimulation/modulation therapies as preventive approaches. Indeed, these therapies are currently only used as symptomatic treatments, and are therefore only initiated once lower urinary tract dysfunctions have been observed. However, in the situation of the spinal cord injury patient, where lower urinary tract dysfunctions are almost systematic, in relation with the emergence of a spinal cord automatism, a preventive approach could probably have its place - to delay or reduce the intensity of lower urinary tract dysfunctions. Electrical stimulation/modulation therapies, because they could promote neuronal plasticity, seem to meet this challenge.

The systematic review, reported according to the PRISMA guidelines, aimed to synthetize the available scientific literature focusing on early interventions to prevent lower urinary tract dysfunctions after acute spinal cord injury. The review identified articles published through April 2021 in the PubMed, Embase, ScienceDirect and Scopus databases with terms regarding early interventions to prevent lower urinary tract dysfunctions after spinal cord injury. Abstract and full-text screenings were performed by three reviewers independently, while two reviewers performed data extraction independently. An article was considered relevant to this literature review if it assessed: an *in-vivo* model of spinal cord injury, including a group undergoing an early intervention compared with at least one control group, and reporting clinical, urodynamic, biological and/or histological data.

Among the 30 studies included in the final synthesis - 9 focused on neurotransmission, 2 on the inflammatory response, 10 on neurotrophicity, 9 on electrical nerve modulation and 1 on multi-system neuroprosthetic training. Overall, 29/30 studies reported significant improvement in urodynamic parameters, regarding both the storage and the emptying phase. These findings were often associated with substantial modifications at bladder and spinal cord level, including up/downregulation of neurotransmitters and related-receptors expression, neural proliferation or axonal sprouting and a reduction of inflammatory response and apoptosis.

The present review therefore supports the concept of early interventions to prevent lower urinary tract dysfunctions after spinal cord injury, particularly through electrical stimulation/modulation therapies.

Response to tibial and sacral neuromodulation in overactive bladder: is there any correlation?

We questioned the relation, in terms of efficacy, between transcutaneous tibial neurostimulation and sacral neuromodulation. Indeed, these two electrical stimulation/modulation therapies can potentially follow each other in our therapeutic algorithms. Clarifying this point could enable us to better support our patients in the shared decision making process. These results may also help us to understand the mechanisms of action of these two therapies. Indeed, for some, these two approaches could be considered as one and the same therapy, with the difference that one directly targets the sacral root, while the other acts at a distance. However, to date, there is no data to confirm or refute this hypothesis.

To assess the correlation between the response to transcutaneous tibial neurostimulation and subsequent response to sacral neuromodulation to treat overactive bladder, all patients who consecutively received transcutaneous tibial neurostimulation followed by a two-stage sacral neuromodulation between January 2016 and June 2022 to treat overactive bladder in two university hospital centers were included. The response to each therapy was evaluated with success defined by a 50% or greater improvement in one or more bothersome urinary symptoms from baseline. The primary endpoint was the statistical relationship between the response to transcutaneous tibial neurostimulation and the response to sacral

neuromodulation, assessed by logistic regression. Secondary endpoints were the statistical relationship between the response to transcutaneous tibial neurostimulation and the response to sacral neuromodulation when controlling for gender, age (< 57 yo vs > 57 yo), presence of an underlying neurological disease, and presence of detrusor overactivity, adding the factor and interaction to the previous regression model.

Among the 92 patients enrolled in the study, 68 of them were women (73.9%), and the median age was 57.0 [41.0-69.0] years. The success was reported in 22 patients (23.9%) under transcutaneous tibial neurostimulation and 66 patients (71.7%) during the sacral neuromodulation test phase. There was no statistical correlation between response to transcutaneous tibial neurostimulation and response to sacral neuromodulation in the overall population ($_{CI95\%}$[0.48; 4.47], p=0.51). Similarly, there was no statistical correlation when controlling for age <57yo or ≥57yo, with p=1.0 and p=0.69, respectively. No statistical study could be conducted for the other subpopulations due to small sample sizes.

We concluded that the response to transcutaneous tibial neurostimulation did not predict the response to sacral neuromodulation in the treatment of overactive bladder; and that transcutaneous tibial neurostimulation and sacral neuromodulation should be considered as distinct therapies in the shared decision making process.

Development of a predictive tool for sacral nerve modulation implantation in the treatment of non-obstructive urinary retention and/or slow urinary stream - a study from the neuro-urology committee of the french association of urology

We questioned the possibility of developing predictive tools, particularly in the context of voiding dysfunction. In this indication, the sacral neuromodulation success rate is highly variable, ranging from 33% to 100% depending on the study. Having such predictive tools at our disposal could enable us to better support our patients in the shared decision making process. These results could also help us better understand the mechanisms of action of sacral neuromodulation as a treatment for voiding dysfunction.

The present work was designed as a retrospective study including all patients who have undergone a two-stage sacral neuromodulation for voiding dysfunction between 2000 and 2021 in 11 academic hospitals. The primary outcome was defined as the definitive

implantation rate. Secondary outcomes included changes in bladder emptying parameters. Univariate and multivariable logistic regression analysis were performed and determined odds ratio for sacral neuromodulation definitive implantation to build a predictive tool. The performance of the multivariable model discrimination was evaluated using the c-statistics and an internal validation was performed using bootstrap resampling.

Of the 357 patients included, 210 (58.8%) were finally implanted. After multivariable logistic regression, 4 predictive factors were found, including age (≤52 yo; OR =3.31 $_{CI95\%}$[1.79; 6.14]), gender (female; OR=2.62 $_{CI95\%}$[1.39; 4.92]), maximal urethral closure pressure (≥70 cmH_2O; OR: 2.36 $_{CI95\%}$[1.17; 4.74]) and the absence of an underlying neurological disease affecting the lower motor neuron (OR =2.25 $_{CI95\%}$[1.07; 4.76]). Combining these factors, we established 16 response profiles with distinct definitive implantation rates, ranging from 8.7% to 81.5%. Internal validation found a good discrimination value (c-statistic, 0.724; $_{95\%CI}$[0.660 to 0.789]) with a low optimism bias (0.013). This allowed us to develop a predictive tool (https://predictivetool.wixsite.com/void).

The present study identified 4 predictive factors, allowing to develop a predictive tool for sacral neuromodulation definitive implantation in patients with voiding dysfunction, that may help in guiding shared decision making process. External validation of the tool is warranted.

Part II: At therapy initiation, Questioning the mechanisms of action

Acute autonomic nervous system response to direct sacral nerve root stimulation in lower urinary tract dysfunction: a new approach to understand the mechanism of action of sacral nerve modulation

We questioned the effect of an acute S3 sacral root stimulation on the balance of the ANS. Indeed, the balance of the ANS seems to be modified, or even altered, in patients with lower urinary tract dysfunctions, particularly in the case of overactive bladder or voiding dysfunction. However, the study of the mechanisms of action of the therapies proposed in these pathological contexts has rarely focused on understanding their effect on the balance of the ANS.

In this retrospective monocentric study, patients undergoing a two-stage sacral neuromodulation for overactive bladder, non-obstructive urinary retention or chronic bladder pain syndrome between March 2022 and June 2023 were analyzed. A standardized stimulation protocol was applied during the lead implantation, each of the four contact points being sequentially stimulated at the amplitude required to elicit anal motor response. Stimulations were labeled as StimA, StimB, StimC, and StimD, ordered by ascending order of minimum amplitude required for anal motor response. Heart rate variability parameters were collected using PhysioDoloris Monitor, and computed through the time-domain (SDNN, RMSSD), the frequency-domain (LF, HF) and the graphical (ANI) methods.

Fifty patients were analyzed, including 35 females. Twelve patients had an underlying neurological disease. Clinical efficacy was deemed achieved in 16/28 patients (57.1%) with overative bladder and in 10/21 patients (47.6%) with non-obstructive urinary retention. SDNN variability significantly increased during stimulation StimA to StimC, while maximum SDNN significantly increased only during stimulation StimA. ANI variability significantly increased during all four stimulations, while maximum ANI significantly increased only during stimulation StimA.

We concluded that direct stimulation of sacral nerve root was responsible for a significant increase in overall ANS activity and in relative para-sympathetic nervous system activity, with a greater effect observed when the stimulation was delivered closer to the sacral nerve root. These results shed light on potential mechanisms of action underlying sacral neuromodulation, particularly regarding the treatment of ANS dysregulation in lower urinary tract dysfunctions.

Part III: After therapy initiation, Questioning the follow-up

Real-life after sacral nerve modulation implantation: rate, reasons, and risk factors for mid-term follow-up discontinuation

We finally questioned the outcomes after sacral neuromodulation definitive implantation, particularly concerning the follow-up. Indeed, even if efficacy and safety of sacral neuromodulation have already been extensively studied, no study has yet investigated follow-up after definitive implantation of the device. However, in view of the few "real-life" data published, including a high rate of loss of efficacy - which may necessitate a revision of the

device, a modification of settings and/or the addition of a concomitant treatment - it now seems more important than ever to question patients' follow-up, to ultimately develop more appropriate care pathways.

In this multicenter retrospective study, all patients who underwent a definitive sacral neuromodulation implantation to treat a lower urinary tract dysfunction between 2014 and 2019 within 6 hospital centers located in the district of "Hauts-de-France" (France) were systematically called during the year 2020 for a standardized (tele)consultation. Patients were divided into 3 distinct profiles according to the regularity of their 5-year postoperative follow-up: "Regular follow-up", "Irregular follow-up" and "Lost to follow-up". The primary outcome was the change in the annual proportion of the 3 follow-up profiles over the 5 years following definitive implantation. As secondary outcomes we described the reasons reported for follow-up discontinuation and looked for risk factors associated with.

Overall, 259 patients were included. At the time of data collection, after a mean follow-up of 28.4 (±19.8) months, 139 patients (53.7%) had a "Regular follow-up", 54 (20.8%) had an "Irregular follow-up" and 66 (25.5%) were "Lost to follow-up". The proportion of patients with a "Regular follow-up" decreased year by year, representing only 46.2% of patients at five-years. 175 patients (67.6%) underwent a standardized (tele)consultation. In multivariate analysis, only "lack of knowledge of the follow-up protocol" was statistically associated with follow-up discontinuation (OR = 5.16 $_{95\%CI}$[2.12; 13.57]). The proportion of patients followed up after definitive sacral neuromodulation implantation decreased steadily over the years, often related to a lack of therapeutic education.

These data suggest the need to build more adapted and efficient care pathways after definitive sacral neuromodulation implantation.

Conclusion

In conclusion, although these data still need to be supplemented by future research projects, they should ultimately enable us to further optimize electrical modulation/stimulation therapies in the management of neurogenic and non-neurogenic lower urinary tract dysfunctions.

SHORT SUMMARY

Even though it corresponds to the alternation between a bladder filling phase and a bladder emptying phase, the normal micturition cycle cannot be summed up as a binary operation but involves the constant consideration of multiple factors: the filling level of the bladder reservoir, the safety of the environment in which we live, the emotional context in which we evolve and the social constraints to which we are subjected.

We now know that there are alterations and/or modifications in brain activity and connectivity, as well as changes in the regulation of the autonomic nervous system (ANS), in certain types of lower urinary tract dysfunctions - notably in overactive bladder or urge urinary incontinence and in certain types of voiding dysfunctions.

Among the therapies available today, electrical modulation/stimulation therapies (tibial neurostimulation and sacral neuromodulation) appear able to normalize and/or modify brain activity and connectivity, as well as the ANS balance. They could thus provide, at least, a partial response to some of the etiopathogenies underlying these lower urinary tract dysfunctions.

However, the deployment and positioning of these electrical modulation/stimulation therapies are still limited by an incomplete understanding of their mechanisms of action, imperfect identification of the indications and populations most likely to benefit from these therapies, a lack of consensus on the setting of the electrical current delivered, and a lack of medium and long-term evaluation.

In the first part, we questioned the indications for these therapies, and particularly their place as a preventive approach for lower urinary tract dysfunctions due to spinal cord injury. We also questioned the relation, in terms of efficacy, between transcutaneous tibial neurostimulation and sacral neuromodulation, to better support patients in shared decision making process. Finally, we developed the first tool to predict the success of sacral neuromodulation as a treatment for voiding dysfunction.

In the second part, we questioned the mechanisms of action, and more specifically the changes in the balance of the ANS in response to an acute sacral root stimulation.

In the third part, we questioned the mid-term follow-up (5 years) after definitive implantation of sacral neuromodulation in a geographic population pool, looking for risk factors for discontinuation of follow-up.

These data, although still to be supplemented by future research projects, will enable us to further optimize electrical modulation/stimulation therapies in the management of neurogenic and non-neurogenic lower urinary tract dysfunctions.

KEYWORDS

Sacral neuromodulation; Tibial neurostimulation; Autonomic nervous system; Overactive bladder; Urinary incontinence; Voiding dysfunction

INTRODUCTION

I. NORMAL REGULATION OF THE LOWER URINARY TRACT

I.1. Regulation of the lower urinary tract, in its simple form

Normal regulation of the lower urinary tract corresponds to the harmonious realization of a micturition cycle alternating between a bladder filling phase and a bladder emptying phase, and ensures two distinct functions, namely:

Comfort, with the possibility of transforming a slow, continuous, autonomous renal secretion into rapid, punctual, conscious bladder emptying, with all the social benefits that this implies.

Safety, by maintaining low pressure in the urinary tract, enabling the kidneys to perform their filtration function, essential for maintaining internal homeostasis.

During the filling phase, the bladder acts as a reservoir, allowing itself to be distended, gradually increasing in volume as urine is secreted by the kidneys. This increase in volume takes place at low pressure, within a compliant bladder reservoir. At the same time, the need to urinate gradually increases. During this phase, the sphincteric complex remains contracted. The filling phase continues until the individual decides to initiate emptying, with the bladder easily reaching a capacity of 300 to 400 mL, corresponding to normal functional bladder capacity.

When the decision is finally made to initiate micturition, the emptying phase can begin. At this point, the sphincteric complex relaxes, and the bladder contracts in a coordinated fashion, allowing the bladder reservoir to empty rapidly, completely and at low pressure.

I.2. Regulation of the lower urinary tract, in all its complexity

Even though it corresponds to the alternation between a bladder filling phase and a bladder emptying phase, the normal micturition cycle cannot be summed up in a binary function, but involves the constant consideration of multiple factors: the level of filling of the bladder reservoir, the safety of the environment in which we live, the emotional context in which we evolve and the social constraints to which we are subjected.

In particular, the initiation of bladder emptying must meet several criteria (1):

- Is emptying **mechanically possible**?
  In other words, is there enough urine in the bladder?
- Is emptying **safe**?
  Primary emotions such as fear are considered. This constraint has enabled us throughout evolutionary history to protect ourselves from potential predators.
- Is emptying **adapted to the emotional context**?
  Secondary emotions such as discomfort are considered.
- Is bladder emptying **adapted to the social context?**
  Social constraints are considered.

A harmonious micturition cycle therefore requires perfect coordination between the bladder and the sphincteric complex, as well as the integration and analysis of numerous contextual factors. These coordination, integration and analysis functions are performed by the nervous system.

We will be focusing on the central nervous system, particularly the cerebral system, as well as the autonomic nervous system (ANS) - positioned as an interface between the central nervous system and the lower urinary tract. By maintaining a balance between the sympathetic (SNS) and parasympathetic (PSNS) nervous systems, the ANS helps maintaining internal homeostasis, as well as regulating the micturition cycle.

I.3. The nervous system and the regulation of the lower urinary tract

During the filling phase - and bladder distension - a number of receptors (notably mechanoreceptors), located in the urothelium and suburothelium, are progressively activated, stimulating sensory afferents (Aδ fibers). These sensory afferents relay nerve impulses along the posterior horn of the spinal cord (spinothalamic pathway) to the supraspinal level, where the information is integrated and processed by multiple cortical and subcortical brain structures. By considering this information, as well as that from other organs and the outside world, the brain can determine at any given moment the response best suited to the context - i.e. to continue the bladder filling phase or initiate the bladder emptying phase. This resultant decision is then transmitted to the Pontine Micturition Center (PMC), located in the brainstem.

The PMC works like a "switch", acting directly on the medullary centers involved in the micturition cycle, thereby activating, or inhibiting them in accordance with the intended response. We distinguish the somatic medullary center (Onulf nucleus) - located in the sacral medulla (S2-S4), the parasympathetic medullary center - also located in the sacral medulla (S2-S4), and the sympathetic medullary center located in the thoracolumbar medulla (T9-L2). Continuation of the bladder filling phase involves activation of the somatic and sympathetic spinal cord centers and inhibition of the parasympathetic medullary center. Conversely, initiation of the bladder emptying phase involves inhibition of the somatic and sympathetic medullary centers and activation of the parasympathetic medullary center (Figure1) (2).

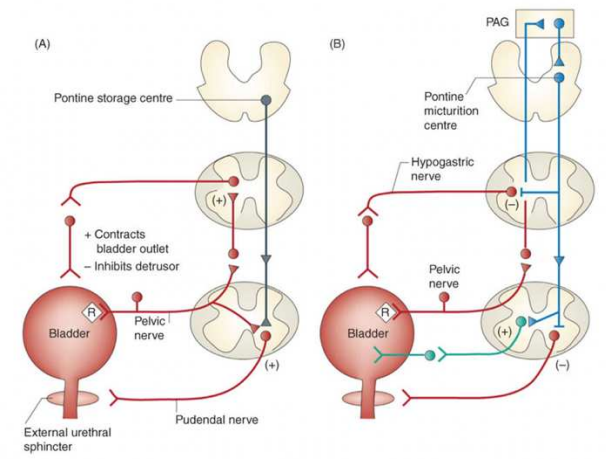

Illustration taken from the publication by De Groat and al (3).

Figure 1: Pontine and medullary circuits involved in the micturition reflex

A: Reflexes involved in continence
B: Reflexes involved in micturition

I.4. Brain structures involved in the regulation of the lower urinary tract

Among the many brain structures - cortical or subcortical - involved in regulating the lower urinary tract, several have been identified using a variety of techniques, including SPECT (single-photon emission computed tomography), and more recently PET (positron emission tomography) and fMRI (functional magnetic resonance imaging).

Among these brain structures, we distinguish (4,5,7):

The periaqueductal gray (PAG), a mesencephalic structure, is considered an anatomical and functional interface between higher brain structures and the brain stem. It receives, processes, and transmits afferent signals from the spinal cord to higher brain structures, where this information is processed. It also receives, coordinates, and transmits efferent signals from higher brain structures to the spinal cord. It plays a major role in adaptive behavioral responses to internal (pain) or external (threat) stressors. The PAG thus has numerous functions, and is notably involved in cardiovascular, respiratory, or motor responses, pain modulation, thermoregulation, and contributes to the mechanisms of arousal and rapid eye movement sleep control.
The PAG is also involved in regulating the lower urinary tract and is even considered the main interface between the afferent and the efferent arms of the micturition. It exerts its control over the lower urinary tract via a specific structure located in the brainstem, the PMC. A recent study by Rijk *et al.* (8) demonstrated that PAG activity increases with bladder filling, but more importantly that the PAG is asymmetrically organized and lateralized, comprising at least three distinct regions. The authors also reported that the internal connectivity of the PAG, particularly between these 3 regions, changed with the sensation of bladder filling.

The Pontine Micturition Center (PMC) is a brainstem structure that acts as a "switch" in the micturition cycle. Mainly under the influence of the PAG, the PMC is able, when activated, to act directly on the medullary centers (somatic, sympathetic and parasympathetic) involved in the micturition reflex.

The limbic system plays a role in behavior and in various emotions such as aggression, moral pain, fear and pleasure, as well as in memory formation. Considered an anatomical and functional interface between cognitive and vegetative life, the limbic system comprises various cortical and subcortical structures, including the **hypothalamus**, fornix, **hippocampus,** amygdala, **cingulate cortex** and **insula**.

The anterior cingulate cortex (ACC), also known as the motor cortex of the ANS, is an important interface between emotion and cognition, specifically in the transformation of our feelings into intention and action.

The insula, also known as the sensory cortex of the ANS or the seat of "interoception", is a subcortical region where sensory information from the viscera is mapped.

The hippocampus belongs to the limbic system, and in addition to its role in memory and spatial navigation, is thought to be involved in behavioral inhibition systems**.**

The hypothalamus, known as a sensor and integrator of peripheral stimuli (hormonal and nervous), is involved in modulating the secretion of hypothalamic hormones. The hypothalamus would be involved in regulating the micturition cycle, notably via the hypothalamic preoptic nucleus, which has direct projections to the PAG and PMC, and would be directly involved in initiating micturition. By integrating a range of peripheral and external stimuli, this structure would inhibit micturition initiation in situations deemed "unsafe" for the organism**.**

The supplementary motor area (SMA) is involved in motor programming and is active during both the planning and execution of complex movements. In addition to its role in coordinating posture and voluntary movements, the SMA therefore plays a role in movement planning.

The frontal lobe, in particular **the ventromedial prefrontal cortex** (vmPFC), is involved in affective and motivational processes, namely the control of the limbic system: inhibition, encoding the motivational value of a stimulus, decision-making and control of reward-based action, mood control, social behavior.

The frontal lobe would also be involved via the **lateral prefrontal cortex** (lPFC), involved in working memory, reasoning, planning and active forms of imagination.

The thalamus, located intermediately between the cortex and the brainstem, is primarily responsible for relaying and integrating sensory afferents and motor efferents, as well as regulating consciousness, vigilance, and sleep. The thalamus plays a crucial modulating role in attention networks and is the "gateway" that determines which sensory and motor information reaches the cortex for processing. Its function in regulating the micturition cycle has yet to be clearly established.

Other brain structures, whose functions are less well established, are also thought to be involved in regulating the micturition cycle**: the parietal cortex, the parieto-frontal cortex, the posterior cortex** (precuneus, posterior cingulate cortex)**, the putamen** and **the cerebellum**.

I.5. Brain circuits involved in the regulation of the lower urinary tract

The brain structures involved in regulating the lower urinary tract enable the "corticalization" of an autonomous function. These structures interact with each other according to specific circuits. In 2015, Griffiths (4) proposed a model including the "micturition reflex" and 3 distinct circuits (Figure 2).

This model, the most recent and comprehensive to date, has the advantage of incorporating the **"Triple Network Model"** concept, comprising 3 networks: the **Default Mode Network** (DMN), the **Salience Network** (SN) and the **Central Executive Network** (CEN).

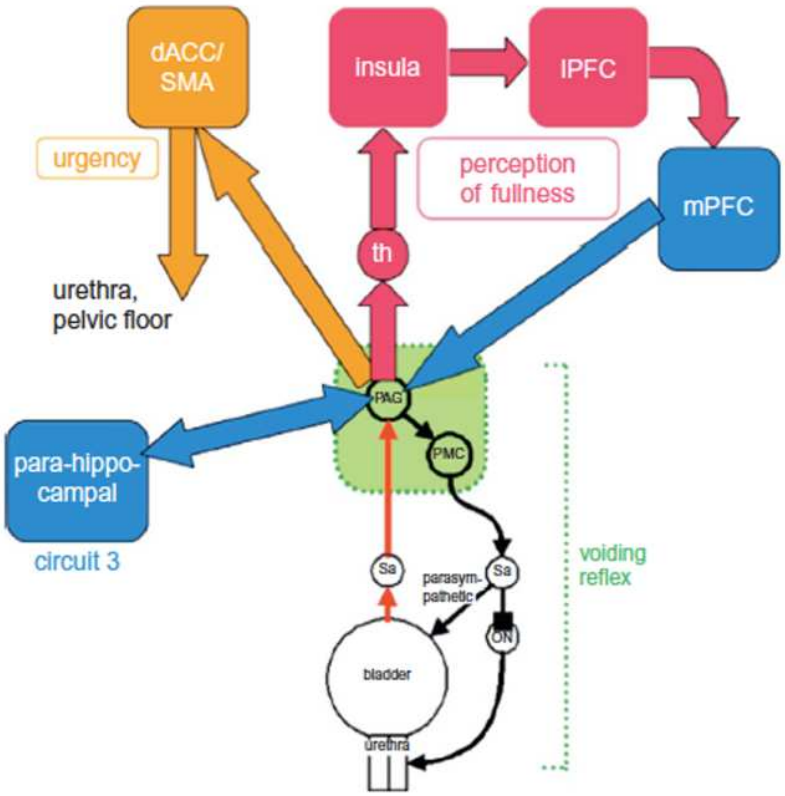

Illustration from Griffiths et al. (4)

Figure 2: Connectivity model (Griffiths) for the regulation of the micturition cycle

The **Central Executive Network** (CEN) is composed mainly of the lPFC and the posterior parietal cortex, around the intraparietal sulcus. It is involved in sustained attention, complex problem-solving and working memory. It is therefore involved in cognition directed towards the outside world.

The **Default Mode Network** (DMN) is made up of the vmPFC, posterior cingulate cortex/precuneus and angular gyrus. It is best known for being active when a person is not focused on the outside world and their brain is in waking repose, such as during daydreaming and mind-wandering. It can also be active during detailed thoughts linked to the performance of external tasks. The DMN is also active at times when the person is thinking about others, thinking about themselves, remembering the past and planning for the future. The DMN is activated at rest and deactivated whenever conscious attention to a task is required. It is therefore involved in cognition directed towards the inner world.

The **Salience Network** (SN) is mainly composed of the insula and the dorsal ACC (dACC). It is involved in the detection and integration of emotional and sensory stimuli, as well as in modulating the transition from inward-directed cognition (DMN) to outward-directed cognition (CEN).

However complete and accomplished, the model proposed by Griffiths (4) remains a simplified model and should be understood as such. It is important to note that this model omits many brain structures (putamen, subthalamic nucleus) and sometimes struggles to arrange certain brain structures within the 4 circuits described (hypothalamus, etc.). Furthermore, one of the 3 components of the **Triple Network Model**, the **Central Executive Network,** is not integrated into this model, or only indirectly, via the evocation of the lPFC.

"Micturition reflex"

It answers the question: "Is bladder emptying **mechanically possible**?"

The "micturition reflex" involves medullary structures, the PMC and the PAG, and is therefore not *strictly speaking* a cerebral circuit. Bladder afferents, stimulated in particular by bladder filling, "ascend" along the posterior horn of the spinal cord (spinothalamic pathway) and converge on the PAG, causing a progressive increase in its activity. When the PAG reaches a certain "threshold" of activity, normally correlated with the level of bladder filling, it is able to activate the PMC. When "activated", the PMC acts directly on the medullary centers involved in micturition, inhibiting the somatic and sympathetic medullary centers and activating the parasympathetic medullary center. These efferent messages initiate and maintain micturition, coordinating relaxation of the sphincteric complex and contraction of the detrusor muscle.

At this level, no bladder feeling is yet conscious, and no voluntary control of the micturition is possible. The "micturition reflex" thus establishes the regulation of the micturition cycle as an autonomous function.

Circuit 1

It answers the question: "Is bladder emptying **adapted to the social context**?"

Circuit 1 mainly involves the vmPFC belonging to the DMN and is thought to act directly on the PAG. Activation of vmPFC would increase PAG activity. Conversely, deactivation of vmPFC would result in a lowering of the PAG activity levels. vmPFC could thus, by regulating the PAG

activity, advance or delay the onset of micturition, but could not, on its own, definitively induce or inhibit micturition.

By integrating social constraints into the regulation of the micturition cycle, Circuit 1 enables the secondary “corticalization” of an initially autonomous function.

***Circuit** 2*

It answers the question: "Is bladder emptying **adapted to the emotional context**?"

Circuit 2 involves the insula, dACC and SMA. The insula, dACC and SMA belong to the SN.

The anterior insula is activated during bladder filling, with a right-hand predominance. This gradually increasing activation could correspond to the normal series of sensations occurring during bladder filling: first sensation of bladder filling (B1), first desire to void (B2) and strong desire to void (B3). In addition, activation of the insula is thought to shift anteriorly as bladder volume and the need to void increase. The dACC and SMA are activated during bladder filling and are thought to be involved in the emergence of the normal and urge sensation to urinate, and in the recruitment of accessory pathways to inhibit the initiation of micturition, by promoting contraction of the sphincteric complex (smooth and striated) and inhibiting contraction of the detrusor muscle.

Circuit 3

It answers the question: "Is bladder emptying **safe**?"

Circuit 3 involves the parahipoccampal complex and may involve the hypothalamus.

As pointed out by Griffiths (4), it is the most hypothetical of the 3 brain circuits described and should be the subject of future work to be confirmed. The parahippocampal complex belongs to the DMN and, like the vmPFC, is thought to act directly on the PAG. Activation of the parahippocampal complex would increase the level of the PAG activity. Conversely, deactivation of the parahippocampal complex leads to a decrease in the PAG activity. Interestingly, the parahippocampal complex, which surrounds the hippocampus, is known to be involved in the retrieval of episodic memories and the recognition of social scenes and contexts.

The hypothalamus is the only structure other than the PAG to act directly on the PMC. It is supposed to provide a "safe" or "unsafe" signal, with the ability to inactivate the PMC when micturition is deemed not "safe" for the organism (9).

I.6. The autonomic nervous system and the regulation of the lower urinary tract

The ANS - through the balance between the SNS and the PSNS - plays a central role in regulating the micturition cycle. Thus, the continuation of the bladder filling phase involves activation of the somatic and sympathetic medullary centers and inhibition of the parasympathetic medullary center. Conversely, initiation of the bladder emptying phase involves inhibition of the somatic and sympathetic medullary centers and activation of the parasympathetic medullary center.

Numerous non-invasive methods can be used to assess ANS activity, in particular overall ANS tone, but also the state of "vegetative balance" - sympathetic or parasympathetic predominance. These methods include heart rate variability (HRV) analysis, sympathetic skin response and pupillometry.

One of the most widely used reference methods in research focusing on lower urinary tract dysfunctions is HRV analysis, i.e. the study of variations in the time intervals between two heartbeats (R-R intervals). Numerous techniques for the spectral or temporal analysis of VFC have been described in the literature (10). Frequency (or spectral) analysis consists of a time-frequency transformation (fast Fourier transform or wavelet transform), and makes it possible to distinguish 3 frequency zones: very low frequencies (VLF) - from 0 to 0.04 Hz - reflecting thermoregulation and endocrine activity; low frequencies (LF) - from 0.04 to 0.15 Hz - reflecting both SNS and PSNS activities associated with the baroreflex; and high frequencies (HF) - from 0.15 to 0.4 Hz - representing absolute PSNS activity. Time domain analysis includes the standard deviation of normal R-R intervals (SDNN) - representing the overall variability of the R-R series; and the root mean square of successive differences between adjacent R-R intervals (RMSSD) - representing short-term variability related to the PSNS.

A recent study conducted at Lille University Hospital as part of a partnership between the Department of Urology, Andrology and Renal Transplantation, the Department of Gynecology and the Center for Clinical Investigation and Technological Innovation (CIC-IT), the results of which have yet to be published, demonstrated the importance of the ANS in regulating the micturition cycle. In this study, we evaluated the ANS response to VFC during urodynamic testing in 30 women with pure stress urinary incontinence due to isolated urethral hypermobility. All patients with other associated lower urinary tract dysfunctions, altered pelvi-perineal sensitivity, a history of pelvi-perineal or spinal cord surgery and/or radiotherapy, or a history of neurological pathology were excluded. We thus demonstrated that, in "healthy" subjects - i.e. with no a priori neurological dysfunction or ANS dysregulation - changes in ANS during bladder filling predicted the occurrence of urodynamic events.
These results support the importance of the ANS as a regulatory interface between brain structures and the lower urinary tract.

II. NEUROGENIC AND NON-NEUROGENIC LOWER URINARY TRACT DYSFUNCTIONS

II.1. From symptoms to lower urinary tract dysfunctions

Lower urinary tract dysfunctions are classically expressed by symptoms, which are investigated during the clinical examination (questioning, physical examination, bladder diary). These symptoms may require further investigations to identify underlying lower urinary tract dysfunctions, to understand their mechanism, and to assess their importance and/or consequences. Complementary investigations include imaging tests (ultrasound, cystography), endoscopic tests (urethro-cystoscopy) and/or urodynamic tests (uroflowmetry, cystometry, urethral profilometry, pressure-flow study).

Lower urinary tract symptoms are classically described according to when they occur in the micturition cycle. A distinction is made between symptoms of the filling phase, symptoms of the emptying phase and symptoms of the post-micturition phase (11).

II.1.a. Symptoms of the filling phase (storage symptoms)

Increased urinary frequency, defined as a complaint that voiding occurs more frequently during waking hours than previously deemed normal by the individual (or caregivers).

Nocturia, defined as an abnormal increase in micturition frequency during the main sleep period. After waking up to urinate for the first time, each micturition must be followed by sleep or an intention to sleep.

Increased bladder filling sensation, defined as a complaint that the sensation of bladder filling occurs earlier or is more intense or persistent to that previously experienced. This phenomenon differs from urgency in that urination may be delayed despite the desire to urinate.

Urgency, defined as a complaint of a sudden, compelling desire to pass urine which is difficult to defer.

According to the International Continence Society (ICS), **urinary incontinence** (UI), defined as a complaint of involuntary loss of urine, comprises 11 distinct entities (11):

- **Urge urinary incontinence (UUI)**, defined as a complaint of involuntary loss of urine associated with urgency.
- **Stress urinary incontinence (SUI)**, defined as a complaint of involuntary loss of urine on effort or physical exertion including sporting activities, or on sneezing or coughing.
- **Mixed urinary incontinence (MUI)**, defined as complaints of both stress and urge urinary incontinence.
- **Enuresis**, defined as a complaint of intermittent (noncontinuous) incontinence that occurs during periods of sleep.
- **Continuous UI**, defined as a complaint of continuous involuntary loss of urine.
- **Insensible UI**, defined as a complaint of urinary incontinence where the individual is aware of urine leakage but unaware of how or when it occurred.
- **Postural UI**, defined as a complaint of urinary incontinence during change of posture or position, for example, from supine or seated to standing.

- **Overflow UI**, defined as a complaint of urinary incontinence in the symptomatic presence of an excessively (over-) full bladder (no cause identified).
- **Disability associated UI**, defined as a complaint of urinary incontinence in the presence of a functional inability to reach a toilet/urinal in time because of a physical (eg, orthopedic, neurological) and/or mental impairment.
- **Sexual arousal-related UI**, defined as a complaint of involuntary loss of urine during sexual arousal, foreplay and/or masturbation.
- **Climacturia**, defined as a complaint of involuntary loss of urine at the time of orgasm.

Overactive bladder syndrome (OAB) is defined as a urinary urgency, usually accompanied by increased day time frequency and/or nocturia, with or without urinary incontinence, in the absence of urinary tract infection or other detectable disease.

II.1.b. Symptoms of the emptying phase (voiding symptoms)

Straining to void, defined as a complaint of the need to make an intensive effort to either initiate, maintain or improve voiding or the urinary stream.

Slow urinary stream, defined as a complaint of a urinary stream perceived as overall slower than previous performance or in comparison with others.

Hesitancy, defined as a complaint of a delay in initiating voiding (when the individual is ready to pass urine).

Terminal dribbling, defined as a complaint that during the final part of voiding there is noticeable slowing of the flow to drops or a trickling stream.

Spraying (splitting) of urinary stream, defined as a complaint that the urine passage is a spray or split rather than a single directional stream.

Position-dependent voiding, defined as a complaint of having to adopt specific positions to be able to void spontaneously or to improve bladder emptying, for example, needing to void in a seated position.

II.1.c. Symptoms of the post-micturition phase (post-voiding symptoms)

Feeling of incomplete (bladder) emptying, defined as a complaint that the bladder does not feel empty after voiding has ceased.

Need to immediately re-void ("Encore" or "Double" voiding), defined as a complaint that further voiding is necessary soon after passing urine.

Post-voiding incontinence, defined as a complaint of a further involuntary passage (incontinence) of urine or dribbling following the completion of voiding.

Post-micturition urgency, defined as a complaint of persistent post-voiding urgency.

For the sake of clarity and conciseness, we will focus exclusively on the symptoms most encountered in clinical practice and for which electrical stimulation/modulation therapies have been most extensively studied:

- **Overactive bladder syndrome – with or without UUI** (OAB/UUI)
- **Voiding dysfunction**, excluding those related to an anatomical bladder outlet obstruction (benign prostatic hypertrophy, urethral stricture).

As mentioned above, lower urinary tract symptoms do not exist in and of themselves and are most often evidence of underlying lower urinary tract dysfunctions, the etiopathogenies of which are manifold.

II.1.d. Etiopathogenies of OAB/UUI

Overactive bladder (OAB) is defined by ICS as the presence of urgency, usually accompanied by daytime frequency and/or nocturia, with or without urinary incontinence, in the absence of urinary tract infection or other detectable disease.
Urge urinary incontinence (UUI) is defined as involuntary loss of urine accompanied or immediately preceded by urgency. **For the sake of simplicity, we will hereafter consider OAB and UUI as a single syndromic entity entitled OAB/UUI.**

Today, it is estimated that OAB/UUI affects 14.4% of the general population in France, with prevalence increasing with age (12).

When there is an injury or a dysfunction of the nervous system, particularly the central nervous system, the terminology used is **"neurogenic OAB/UUI".** In this case, lower urinary tract symptoms are directly linked to impaired cerebral inhibitory control (brain lesion), or to the inability of cerebral structures to exert inhibitory control over the spinal cord (spinal cord lesion). Alteration or inoperability of cerebral inhibitory structures thus leads to a loss of inhibition of the micturition reflex, marked by the onset of urgency, generally accompanied by daytime frequency, nocturia and sometimes even UUI (Figure 3) (13).

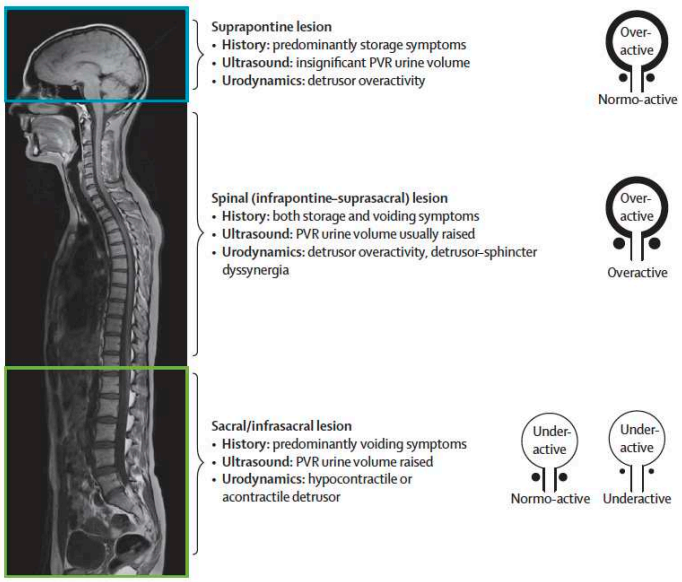

Illustration from Panicker et al. (13)

Figure 3:
Type of lower urinary tract dysfunction according to the localization of the neurological lesion.

When no injury or dysfunction of the nervous system has been identified, the terminology used is **"non-neurogenic OAB/UUI".** Not least because it is multifactorial, the etiopathogenic understanding of non-neurogenic OAB/UUI is complex. Thus, Peyronnet *et al.* (14), in a recent review of the literature synthesizing all the etiopathogenies evoked for OAB/UUI, concluded that non-neurogenic OAB/UUI rather than being considered "idiopathic" - meaning a condition that is defined in itself and is neither the consequence nor the complication of another - should be considered a *"complex, multifactorial symptomatic syndrome, resulting from multiple* potential *pathophysiological mechanisms".* Among the underlying etiopathologies explored, the authors mentioned alterations in the functioning of the detrusor muscle (myogenic), the urothelium/sub-urothelium, the urethra (uretrogenic), as well as cortical and subcortical structures (excluding any neurological pathology). The authors also stressed the importance of other pathophysiological factors including metabolic syndrome, affective disorders, sex hormone deficiency, urinary microbiota, functional gastrointestinal disorders and subclinical ANS dysfunction (Figure 4) (14).

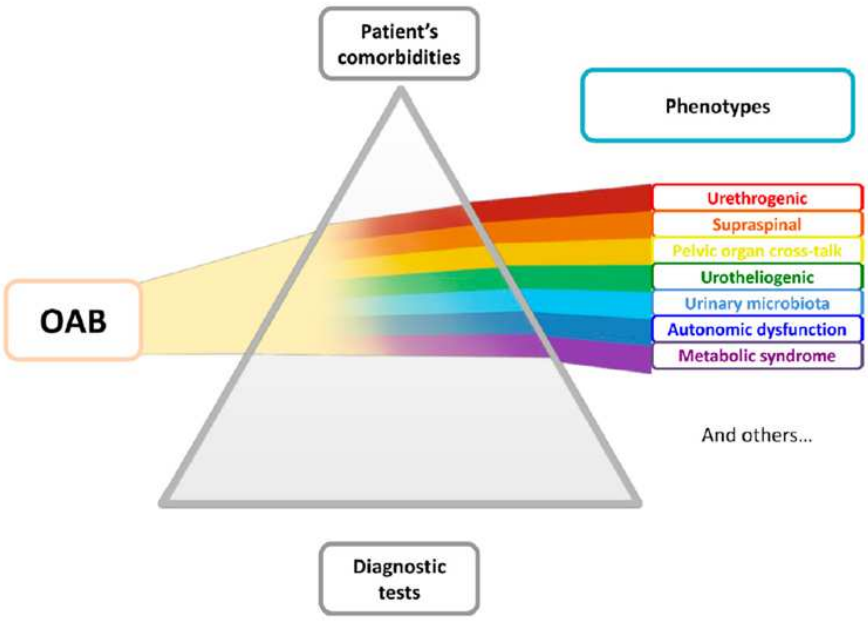

Illustration from Peyronnet et al. (14)

Figure 4: The "prismatic" diagnostic approach to OAB/UUI proposed by Peyronnet *et al*. (14)

II.1.e. Etiopathogenies of voiding dysfunction

Voiding dysfunction, which in extreme cases may present as an acute urinary retention or even an overflow urinary incontinence, is defined by the ICS as an abnormally slow and/or incomplete bladder emptying, manifested by an abnormally slow urine flow and/or an abnormally high post-void residual (11).

As the definition of voiding dysfunction is based on urodynamic criteria - unlike OAB/UUI, whose definition is based on symptoms - it is difficult today to estimate its prevalence in the general population (15).

Voiding dysfunction can be the result of two distinct mechanisms. It may be secondary to a failure of detrusor muscle contraction and/or the presence of a bladder outlet obstruction. This bladder outlet obstruction may be anatomical (benign prostatic hypertrophy, urethral stricture) or functional (failure of bladder neck opening, failure of relaxation of the striated sphincter, detrusor-sphincter dyssynergia).

When there is an injury or dysfunction of the nervous system, the terminology used is **"neurogenic voiding dysfunction".** In the case of brain lesion, voiding dysfunction, although rare, may be secondary to a lack of sphincter relaxation at the time of micturition, probably due to the reinforcement of certain inhibitory cerebral structures. In the case of spinal cord injury, voiding dysfunction is nearly systematic and correspond to a detrusor-sphincter dyssynergia secondary to the emergence of a medullary automatism. When the sacral roots or peripheral nerves are involved, voiding dysfunction is secondary to impaired bladder sensitivity and detrusor contractility. It may sometimes be associated with urinary incontinence due to sphincter insufficiency (Figure 3) (13).

When no injury or dysfunction of the nervous system has been identified, the terminology used is **"non-neurogenic voiding dysfunction".** Apart from situations where an anatomical bladder outlet obstruction is identified - benign prostatic hypertrophy, urethral stricture - the etiopathogenic understanding of voiding dysfunction is also complex.

In cases of detrusor hypocontractility, several etiopathogenies have been proposed, and summarized in a literature review by Osman *et al.* (15). Among the hypotheses put forward are altered detrusor muscle function (myogenic), disturbances in cortical and subcortical structures (excluding any neurological pathology), as well as iatrogenic causes arising from medical treatments (opiates, neuroleptics, anticholinergics) and surgical procedures (pelvic interventions). Furthermore, it should be emphasized that detrusor hypocontractility appears to be an inherent component of the physiological aging process, manifesting itself independently of any specific pathological condition.

Since male urology has mainly focused on the involvement of benign prostatic hypertrophy, the data we have concerning voiding dysfunction secondary to a bladder outlet obstruction are mainly issued from the female population. In a 2014 literature review, King and Goldman reported 3 mechanisms underlying bladder outlet obstruction in women, including dysfunctional voiding, Clara Fowler syndrome and bladder neck obstruction (16).

Dysfunctional voiding is defined by the presence of an intermittent urinary stream associated with intermittent involuntary contraction of the striated sphincter or levator ani, in the absence of any neurological pathology. Several etiologies have been proposed to explain the development of dysfunctional voiding, including the "*high incidence of internal stress within families*" during the transition from reflex micturition in childhood to normal voluntary micturition in adulthood, with a strong correlation between anxiety, depression, and the development of dysfunctional voiding. For other authors, dysfunctional voiding could correspond to an adaptive guarding reflex response in pre-existing OAB/UUI, where the external sphincter reacts initially to involuntary detrusor contraction or sensory urgency, with the response generalizing secondarily to voluntary micturition. Behavioral etiology in patients with infrequent micturition has also been suggested.

Clara Fowler syndrome, first described in 1988, occurs in young women with no known etiology for voiding dysfunction (17). Diagnosis is confirmed by the presence of specific electromyographic abnormalities of the striated sphincter of the urethra (decelerating bursts, complex repetitive discharges), increased urethral pressure and the frequent presence of polycystic ovaries.

Obstruction of the bladder neck is defined by the presence of high intra-detrusor pressures associated with a slow urinary stream, and the demonstration of a closed bladder neck on per voiding cystography associated with a normo-functional striated urethral sphincter. Since its first description in 1959 in children (18), then in 1984 in adult women (19), several etiopathogenies have been proposed. Among the hypotheses put forward are fibrosis, hypertrophy, or abnormal configuration of the smooth musculature, and more recently an abnormal increase in sympathetic activity of the bladder neck.

II.2. Lower urinary tract dysfunctions and the activity of brain structures

The study of the activity of brain structures and their relationship to lower urinary tract dysfunctions has focused mainly on female non-neurogenic OAB/UUI, and almost exclusively by means of brain fMRI.

Within the central nervous system, and more specifically at brain level, several regions of interest have been identified in fMRI as being involved during the normal micturition cycle and in pathological situations such as OAB/UUI. The main regions of interest were reported by Tadic *et al.* as early as 2008 (20). Since then, several studies aimed at identifying these regions of interest have added to or clarified these data, sometimes with contradictory results (9,21–25).

In patients with OAB, however, it is possible to note that high bladder filling is associated with greater activation of cerebral networks, compared with control patients, particularly in the DMN and SN, with greater activation of the following structures: for the DMN, the posterior cingulate cortex, the precuneus and the lPFC; for the SN, the dACC and the anterior insula (24).

In patients with UUI subjected to high bladder filling, increased activation of other structures has also been reported, such as primary motor cortex (right), visual cortex (bilateral), posterior insula (left) with extension to auditory cortex and parahippocampal gyrus (right) with extension to cerebellum (9).

Of all these regions of interest, the **anterior cingulate gyrus** (particularly the dACC), **insula** and **frontal cortex** are those whose increased activation during bladder filling has been most frequently reported in women with OAB/UUI (21).

Activation of these regions of interest also appears to vary according to the degree of bladder filling (23). Thus, at low bladder filling, the insula is more extensively activated - mainly on the right, in patients with OAB, compared with control patients. During high bladder filling, the dACC is predominantly activated in OAB patients, whereas it is not in control patients. For Griffiths *et al.* (25), the increased activation of dACC during the strong desire to void is probably linked to the recruitment of accessory pathways that inhibit the initiation of micturition.

To our knowledge, only one study has investigated the link between the activity of brain structures and voiding dysfunction in multiple sclerosis (MS) patients, using brain fMRI.

This study was published by Khavari *and al.* in 2020 (26). The authors assessed the activity of brain structures in 28 women with MS: 14 with no voiding dysfunction (group 1) and 14 with voiding dysfunction (group 2). The authors reported that, at the time of attempted micturition initiation, group 2 had significantly lower activation levels in all areas of interest, except for the left cerebellum and right cingulate gyrus. Group 2 also showed deactivation of the right and left PMC, right PAG, left thalamus and left cingulate gyrus, while Group 1 showed activation of these regions.

Taken together, these data suggest abnormally high activation of certain structures during bladder filling in patients with non-neurogenic OAB/UUI. These brain structures are involved in regulating the need for micturition, but also, during high bladder filling, in the recruitment of accessory pathways, notably allowing contraction of the pelvic floor, and most likely aimed at preventing micturition as a last resort.

In addition, a single study in women with MS suggests that bladder emptying disorders are associated with an abnormal decrease in the activity of certain brain structures - notably those involved in the initiation of micturition.

II.3. Lower urinary tract dysfunctions and brain connectivity

When talking about brain connectivity, we need to distinguish between structural connectivity, functional connectivity, and effective connectivity.

Structural connectivity represents the anatomical connection between distinct brain regions - through the study of white matter tracts.
Functional connectivity represents the temporal synchronization (or correlation) of activity fluctuations between distinct brain regions, reflecting their level of functional communication.
Effective connectivity represents causal interactions relating to a task and information flows.

The study of brain connectivity and its relation to lower urinary tract dysfunctions has focused mainly on female non-neurogenic OAB/UUI, and exclusively by means of fMRI.

Data on functional connectivity, both in the context of the normal micturition cycle and in pathological situations such as OAB/UUI , were reported by Tadic *et al*. as early as 2008 (20). Since then, several studies describing functional connectivity have added to or clarified these data, sometimes with contradictory results (9,21–25).

In healthy patients, however, it is possible to conclude that there are connections, most probably inhibitory, between the right insula and/or the dACC and numerous brain regions that respond to bladder filling: the frontotemporal region, the thalamus, the putamen, the cerebellum and the PAG (20).

In women with UUI, the connections of the right insula and/or the dACC differ, with connections directed to other structures, including the parieto-temporal cortex, the parahipoccampal gyrus and certain regions of the cerebellum, usually involved in the control of pelvic floor contraction, suggesting the recruitment of accessory pathways to inhibit the initiation of micturition (9,20).

Nardos *et al.* (27) furthermore, succeeded in isolating distinct functional connectivity patterns specific to patients with UUI, connecting:

- Autonomic and cognitive control centers (dorsal/ventral ACC) as well as default regions (angular gyrus and ventral medial frontal regions) to primary and supplementary motor areas likely to be involved in pelvic floor contractions.
- Cognitive/executive control centers (superior frontal gyrus) and regions such as the cerebellum, involved in complex functions covering motor control during pelvic floor contractions as well as cognitive functions such as attention and the regulation of fear and pleasure.
- The visceral-sensory processing center (insula) and part of the supplementary motor area (para-central lobule).

Interestingly, according to Griffiths *et al. (22),* in patients with UUI, fMRI reported either deactivation of circuits 1 and 3 (belonging to the DMN), or activation of circuit 2 (belonging to the SN), but rarely both at the same time.

A few studies have also studied the relation between brain connectivity and voiding dysfunction in patients with MS (28–33)**.**

In a study published in 2022, Shi *et al. (32)* assessed the functional brain connectivity between 17 regions of interest known to participate in the strong desire to void and/or the initiation of micturition by comparing 9 women with MS and 10 control women. The authors reported that, at the time of "urge to void", control women showed significantly greater functional connectivity in regions involved in bladder filling and micturition suppression than women with MS. These regions included the bilateral anterior cingulate cortex, the right SMA and the right middle frontal gyrus. The authors also reported that during the attempted initiation of micturition, control women showed significantly stronger functional connectivity in the right inferior frontal gyrus compared with MS women.

In 2023, Tran *et al. (33)* from the same research team, assessed functional and structural brain connectivity in 27 women with MS-related voiding dysfunction. The women were divided into two distinct groups according to their ability to empty the bladder. Group 1 included 14 women with preserved spontaneous micturition with PVR<40% of bladder capacity. Group 2 comprised 13 women who could no longer urinate spontaneously or had an PVR≧40% of bladder capacity. Although the authors' main objective was to determine how functional and structural brain connectivity data could be used to classify voiding dysfunction in MS women using "machine learning" techniques, they nevertheless came up with some particularly interesting results. When information on grey matter (functional connectivity) and white matter (structural connectivity) was combined as input data to evaluate the machine learning algorithms, the 10 values with the best predictive value all turned out to be grey matter-related (functional connectivity). In parallel, the authors reported that the right superior longitudinal fasciculus proved to be the white matter tract (structural connectivity) best able to predict the type of voiding dysfunction. After noting that connectivity at the level of the right superior longitudinal fasciculus was ranked only 16th in terms of its ability to predict voiding dysfunction, the authors concluded that structural connectivity was more persistent and stable, where functional connectivity was more dynamic. The authors suggested that functional connectivity was susceptible to adaptation, notably through the establishment of new connections (neural plasticity) within the neural network involved in micturition initiation. This hypothesis is reinforced by the observation of stronger functional connectivity in women who maintained spontaneous micturition, suggesting that even if white matter is affected in MS, new functional connections are probably able to form in order to compensate for and maintain normal initiation of micturition.

Taken together, these data suggest a modification of cerebral functional connectivity in patients with non-neurogenic OAB/UUI, with an alteration in inhibitory connections associated with the appearance of specific connectivity patterns most likely aimed at preventing the occurrence of micturition as a last resort, by recruiting areas involved in pelvic floor contraction and cognitive functions related to attention.

In addition, distinct patterns of functional connectivity have been demonstrated between patients with UUI, suggesting the existence of multiple etiopathogenies for OAB/UUI, visible at the brain level.

From a few studies carried out in women with MS, it seems that voiding dysfunction is associated with reduced functional connectivity between brain structures involved in initiating micturition. Furthermore, it seems that in this specific context - where structural connectivity may be compromised by the accumulation of white matter lesions - neuroplasticity may enable, at least partially, the re-establishment of functional connectivity to keep micturition initiation possible.

II.4 Lower urinary tract dysfunctions and the autonomic nervous system

The study of ANS activity and its relationship with lower urinary tract dysfunctions has focused mainly on female non-neurogenic OAB/UUI, most often by means of HRV studies. Studies of sympathetic skin response and pupillometry have been used more marginally.

Heart rate variability analysis is the study of variations in the time intervals between two heartbeats (R-R intervals). Numerous techniques for the spectral or temporal analysis of HRV have been described in the literature (10). Frequency (or spectral) analysis consists of a time-frequency transformation (fast Fourier transform or wavelet transform), and makes it possible to distinguish 3 frequency zones: very low frequencies (VLF) - from 0 to 0.04 Hz - reflecting thermoregulation and endocrine activity; low frequencies (LF) - from 0.04 to 0.15 Hz - reflecting both SNS and PSNS activities associated with the baroreflex; and high frequencies (HF) - from 0.15 to 0.4 Hz - representing absolute PSNS activity. Time domain analysis includes the standard deviation of normal R-R intervals (SDNN), which represents the overall variability of the R-R series, and the root mean square of successive differences between adjacent R-R intervals (RMSSD), which represents short-term variability related to the PSNS.

In 2001, Blanc *et al. (34)* were the first to assess HRV from an electrocardiogram (ECG) performed for 24 consecutive hours in 11 women with SUI, 5 women with UUI and 9 women with MUI. In women with MUI or UUI, the authors reported an overall decrease in HRV compared with women with SUI. Furthermore, in women with UUI, temporal indices showed a decrease in PSNS modulation, and frequency indices a decrease in SNS modulation.

Similar results were reported in 2005 by Choi *et al.* (35) in a study of 40 women with OAB and 40 control women using a 5-minute ECG recorded on an empty bladder. The authors reported a significant decrease in SDNN (27.5 ± 13.35 *vs.* 36.0 ± 14.28; p = 0.002), RMSSD (23.4 ± 11.92 *vs.* 30.4 ± 17.18; p = 0.012) and HF (184.7± 239.20 *vs.* 268.1 ± 328.97; p = 0.048) in women with OAB compared with controls. These results demonstrate a decrease in overall ANS activity associated with a decrease in PSNS activity, in an empty bladder situation, in women with OAB compared with control women.

In 2007, Hubeaux *et al. (36)* evaluated HRV from an ECG recorded during a filling cystometry in 7 women with pure SUI and 3 women with OAB. HRV parameters were analyzed over 5 distinct periods R0 to R4, where R0 corresponded to an empty bladder, R1 corresponded to the period from the start of bladder filling to the first desire to void, R2 corresponded to the period from the first desire to void before the onset of the strong desire to void, R3 corresponded to the period before the onset of the strong desire to void to the onset of the strong desire to void, and R4 corresponded to the period following the onset of the strong desire to void. In women with pure SUI, the authors observed no significant change in HRV. On the other hand, in the 3 women with OAB, the authors reported a significant decrease in HF between R0 and R4 (p = 0.029) and between R3 and R4 (p = 0.022). They also reported a significant increase in LF between R0 and R4 (p = 0.0001) and R3 and R4 (p = 0.043). Similarly, the authors reported a significant increase in the LF/HF ratio between R0 and R4 (p = 0.018) and between R3 and R4 (p = 0.034). These results demostrate a decrease in PSNS activity associated with a probable increase in SNS activity during bladder filling in women with OAB compared with women with pure SUI.

Similarly, in 2010, Kim *et al*. (37) assessed the HRV from an ECG recorded at rest after bladder filling to a volume of 100mL in 29 women with UUI and 47 women with pure SUI. The authors reported a significant increase in the LH/HF ratio (3.5 ± 3.6 vs. 1.6 ± 1.1; p <0.05) in women with UUI compared with women with pure SUI. Again, the results demonstrate a decrease in PSNS activity associated with a probable increase in SNS activity after 100 mL bladder filling in women with UUI compared with women with pure SUI.

In a more recent study, published in 2023, Chen *et al. (38)* evaluated the sympathetic skin response and HRV from a neuECG (a device enabling simultaneous non-invasive recording of the electrocardiogram and the sympathetic skin response (39)) recorded in the morning at rest in 23 patients with OAB and in 29 control patients. Like other authors previously, they reported a significant decrease in SDNN (31.94 ± 12.61 *vs.* 41.08 ± 18.19; p = 0.046), RMSSD (25.28 ± 11.65 *vs.* 33.86 ± 17.51; p = 0.049) and HF (0.54 ± 0.15 *vs.* 0.64 ± 0.18; p = 0.035) as well as a significant increase in LF (0.46 ± 0.15 *vs.* 0.36 ± 0.18; p = 0.035) in patients with OAB compared with control patients. They further demonstrated that the sympathetic cutaneous response was significantly higher (1.08 ± 0.37 *vs.* 0.81 ± 0.24; p = 0.003) at rest in patients with OAB compared with control patients. Interestingly, they also demonstrated that the sympathetic cutaneous response was the most suitable parameter for predicting the presence of OAB (AUC = 0.783; p < 0.001). These results point to an increase in SNS activity in the morning at rest in patients with OAB compared with control patients.

Two studies, one using HRV (40) and the other using pupillometry (41), reported conflicting results in patients with OAB/UUI, showing increased PSNS activity at rest.

Thus, in 2012, Ben-Dror *et al. (40)* assessed HRV from an ECG recorded during a standardized physiological bladder filling, namely a 1.5L water intake at a frequency of 250 mL/min. HRV parameters were assessed at the different needs felt by the women, including empty bladder, first sensation of bladder filling (B1), first desire to void (B2), strong desire to void (B3) and maximum bladder capacity. After including 9 women with OAB and 15 control women, the authors reported that during the bladder-filling phase, women with OAB had significantly lower LF values compared with control women (p = 0.02). Furthermore, in control women, LF increased continuously, whereas in women with OAB, LF increased until the first desire to void, then decreased sharply to baseline values. Contrary to previous reports, the results show that women with OAB have reduced ANS activity than control women, throughout the entire bladder filling process. In addition, these results also show an abrupt decrease in ANS activity after the first desire to void.

Aydogmus *et al. (41)* were the only ones to assess ANS activity using pupillometry, comparing 40 women with OAB/UUI and 40 control women. Pupillometry was performed at rest between 10 am and 12 am. The authors reported a significant decrease in pupillary diameter in women with OAB/UUI (5.03 mm ± 0.79 vs. 5.58 mm ± 0.51; p = 0.007), as well as a significant increase

in dilation latency (967.60 ms ± 303.77 vs. 851.32 ms ± 97.09 ; p = 0.028) and contraction latency (300.70 ms ± 92.23 vs. 263.37 ms ± 56.87; p = 0.029) of the pupil, associated with a significant increase in pupil contraction duration (733.15 ms ± 341.97 vs. 587.99 ± 96.35; p = 0.021). These results demonstrate an increase in morning PSNS activity at rest in women with OAB/UUI compared with control women.

To our knowledge, only one study has evaluated ANS activity in the context of voiding dysfunction.

This study was published by Amarenco *et al*. in 2006 (42). The authors studied ANS activity in 10 women with Clara Fowler syndrome. The ANS was studied using 5 tests of cardiovascular autonomic function, including the HRV during deep breathing, the cold pressure test, the Valsalva ratio, the blood pressure response to standing and the measurement of the sympathetic cutaneous response. Of the 10 women included, 6 had more than 2 positive tests, and were considered to have dysautonomia, with no apparent signs of dysautonomia in daily life (blurred vision, pupil abnormalities, clinical manifestations of orthostatic hypotension, gastrointestinal symptoms). The authors concluded that occult dysautonomia is frequently present in women with Clara Fowler syndrome.

Taken together, these data suggest a modification in the balance of the ANS in patients with OAB/UUI in a variety of situations - whether at rest, during empty bladder state, or during physiological or artificial bladder filling - with consistently, although some data may be contradictory - a decrease in PSNS activity associated with a probable increase in SNS activity compared to "healthy" patients or those with pure SUI.

Based solely on data from a series of patients with Clara Fowler syndrome, it is only possible today to envisage occult dysautonomic involvement as an etiopathogenesis underlying certain types of voiding dysfunction.

III. MANAGEMENT OF NEUROGENIC AND NON-NEUROGENIC LOWER URINART TRACT DYSFUNCTIONS

The management of lower urinary tract dysfunctions aims to achieve two objectives: **improving quality of life** - by reducing the intensity and frequency of lower urinary tract symptoms and **protecting the upper urinary tract** - by restoring lower urinary tract function and protecting the upper urinary tract from high pressure. Furthermore, in the context of neurogenic lower urinary tract dysfunctions, **improving autonomy** in patients with limited functional capacity is an additional objective.

III.1. Management algorithm for neurogenic and non-neurogenic OAB/UUI

It is important to note that protection of the upper urinary tract is not a major issue in the management of non-neurogenic OAB/UUI. However, in the context of neurogenic OAB/UUI - particularly in patients with spinal cord injury - protection of the upper urinary tract, by achieving a low-pressure filling phase - decreasing detrusor hyperactivity and bladder compliance disorders - must be considered a priority objective.

Even if national and international guidelines are not strictly similar today (43,44), it is possible to reach a consensus regarding the management of neurogenic and non-neurogenic OAB/UUI in France as an algorithm comprising 4 successive lines of treatments (Figure 5).

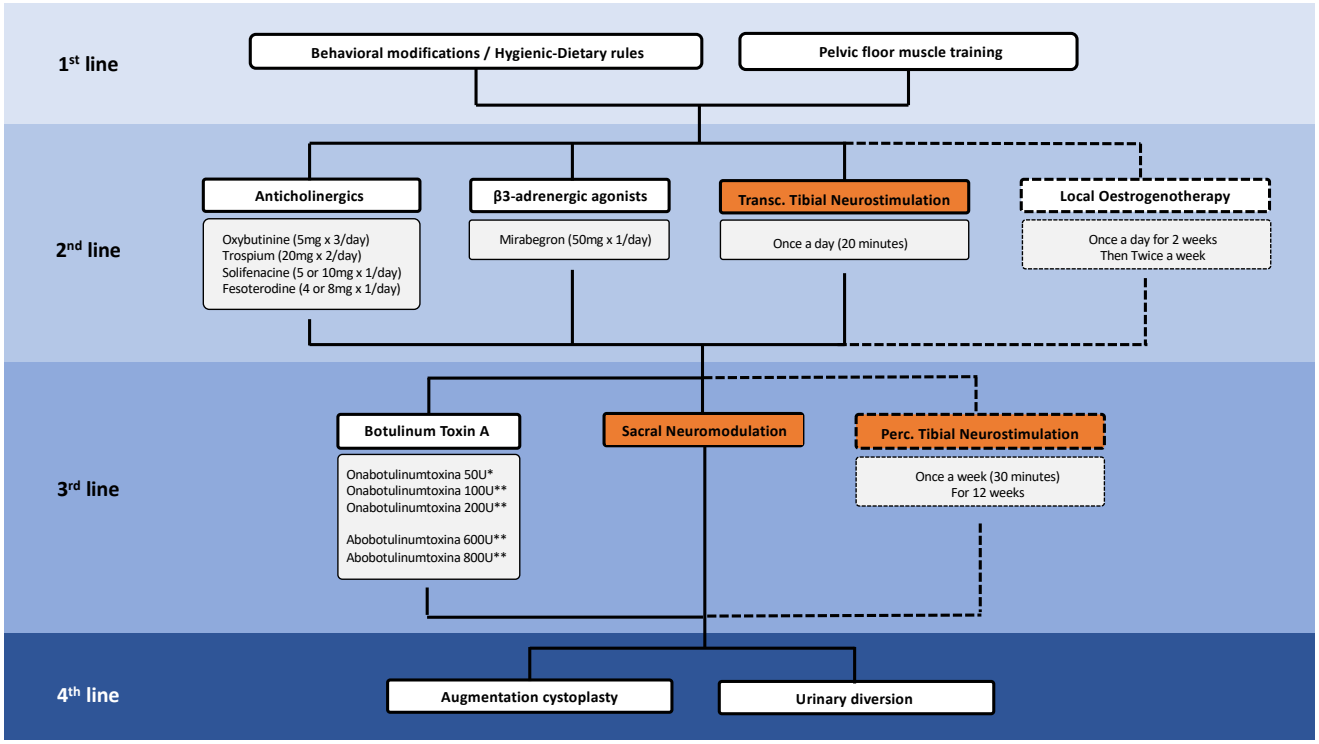

Figure 5: Management algorithm for OAB/UUI (synthesis of national and international recommendations).

* Marketing authorization for non-neurogenic OAB/UUI
** Marketing authorization for non-neurogenic and neurogenic OAB/UUI - multiple sclerosis with spontaneous micturition
*** Marketing authorization for neurogenic OAB/UUI - spinal cord injury and multiple sclerosis with clean intermittent self-catheterization
In Orange: The therapies studied in the present thesis.

III.1.a. First-line treatments for neurogenic and non-neurogenic OAB/UUI

The first line of treatment includes behavioral modification and the application of hygienic-dietary rules, as well as pelvic floor muscle training.

It is important to note that this first-line approach is rarely used in the management of neurogenic OAB/UUI. Indeed, even if behavioral modifications and the application of hygienic and dietary rules always make sense, they are rarely sufficient on their own to control symptoms and protect the upper urinary tract. In addition, pelvic floor muscle training requires the integrity of sensory and motor neurological pathways. As a result, even if pelvic floor muscle training can be proposed in rare cases - notably in the context of incipient multiple sclerosis - it can rarely act on neurogenic lower urinary tract dysfunctions.

III.1.b. Second-line treatments for neurogenic and non-neurogenic OAB/UUI

The second line includes drug treatments such as anticholinergics or β3-adrenergic agonists, as well as tibial neurostimulation in some cases.
In addition, in the specific context of genitourinary syndrome of menopause (GSM), local estrogen therapy can also be proposed, with particularly interesting results in terms of efficacy and safety (45). This therapy, considered as the treatment for GSM, will not be specifically addressed here.

Anticholinergics act at the postsynaptic level, competitively preventing acetylcholine binding to muscarinic receptors located in the urothelium, suburothelium and detrusor, and involved in bladder sensitivity and detrusor contractility. In France, 4 molecules can be prescribed for this indication: Oxybutinin (5mg x 3/day), Trospium (20mg x 2 day), Solifenacin (5 or 10mg x 1/day), Fesoterodin (4 or 8mg x 1/day).

In the context of non-neurogenic OAB/UUI, they enable significant improvement in 44% to 89% of cases at 12 weeks (46,47). In terms of safety, since acetylcholine is distributed ubiquitously throughout the body, side effects are frequent, and include dry mouth, dry eyes, constipation and worsening of pre-existing cognitive disorders or voiding dysfunction (48). Anticholinergics are discontinued in the first two years following prescription in 85% to 90% of cases, due to lack of efficacy and/or poor tolerance (49).

In the context of neurogenic OAB/UUI (50) , in addition to improving lower urinary tract symptoms, they stabilize detrusor activity by delaying and reducing uninhibited detrusor contractions, thus protecting the upper urinary tract. In this specific context, anticholinergic treatments are sometimes used at higher doses, sometimes even in dual therapy, with tolerability often better than in the non-neurogenic population.

β3-adrenergic agonists act at the postsynaptic level by stimulating β3 receptors located in the urothelium and detrusor and involved in detrusor relaxation. Introduced to the French market in 2016, Mirabegron is the only molecule in this therapeutic class that can currently be

prescribed for this indication. However, in 2024, it is still not reimbursed by public health insurance, considerably limiting its use in everyday clinical practice.

In the context of non-neurogenic OAB/UUI, β3-adrenergic agonists show efficacy similar to that observed with anticholinergics but associated with a better safety profile (51). However, this does not prevent β3-adrenergic agonists from being discontinued early, with treatment suspended in around 70% of cases in the first two years following their prescription (52).

In the context of neurogenic OAB/UUI, although Mirabegron appears to have similar efficacy to anticholinergics in terms of symptoms, the same is probably not true for urodynamic parameters (53). Indeed, Welk *et al.* (54) conducted a randomized clinical trial comparing Mirabegron with placebo in spinal cord injury and MS patients and concluded that there was no urodynamic improvement associated with Mirabegron in the neurological population. Further studies will of course be needed to confirm these results.

Transcutaneous tibial neurostimulation, considered a minimally invasive electrical stimulation therapy self-administered at home, has seen its use gradually increase over the last two decades, particularly in France. Its positioning as a second-line therapy in national and international recommendations - particularly in populations at risk of poor drug tolerance (55) - is, however, recent and not recognized by all (43). This therapy will be developed in greater detail in a dedicated section (Cf *IV. ELECTRICAL STIMULATION/MODULATION THERAPIES*).

III.1.c. Third-line treatments for neurogenic and non-neurogenic OAB/UUI

The third line includes intra-vesical injections of botulinum toxin A and sacral neuromodulation, as well as percutaneous tibial neurostimulation (outside France).

Intra-vesical injections of botulinum toxin A act at the presynaptic level, blocking acetylcholine release mechanisms at muscarinic receptors located in the urothelium, sub-urothelium and detrusor and involved in bladder sensitivity and detrusor contractility. The effect is temporary and requires regular repetition of intra-vesical injections every 6 to 12

months. In France, 2 molecules are available for intra-detrusor injection: onabotulinumtoxina and abobotulinumtoxina.

In the context of non-neurogenic OAB/UUI, onabotulinumtoxina 50U and 100U obtained marketing authorization in France in 2014 under the following heading: *"Idiopathic overactive bladder associated with symptoms including 3 episodes of urinary incontinence with urgency over 3 days and urinary frequency defined by a number of micturitions ≥ 8 per day and not responding adequately to anticholinergics (after 3 months of treatment) or intolerant to anticholinergic treatment and not responding to well-conducted physiotherapy"*. The randomized phase 3 trial published by Nitti *et al.* in 2013 (56), which led to this marketing authorization, reported a significant reduction in UUI episodes at 12 weeks post-injection, averaging -2.65 episodes/day for onabotulinumtoxina 100U, versus -0.87 episodes/day for placebo. This reduction in UUI episodes was associated with a significant improvement in symptoms (KHQ self-questionnaire) and quality of life (I-QOL self-questionnaire). In terms of safety, the urinary tract infection rate at 12 weeks was almost multiplied by 3 (15.5%) compared with placebo (5.9%). In addition, an episode of urinary retention was reported in 5.4% of patients within 12 weeks of the injection, and during this time, 6.1% of patients had to initiate clean intermittent self-catheterization (CISC) - whether permanently or not. It also appears that this therapy is rarely continued over the long term, with discontinuation of injections ranging from 63% to 71% within 3 years of the first injection (57,58). In these two studies, discontinuation was most often motivated by poor tolerance in patients with recurrent urinary tract infections and/or voiding dysfunction requiring CISC.

In the context of neurogenic OAB/UUI, onabotulinumtoxina 200U obtained its first marketing authorization in France in 2011 under the following heading: *"Bladder hyperactivity due to problems associated with spinal cord injury or multiple sclerosis, leading to urinary leakage (involuntary emission of urine during the day or night)". It is* interesting to note that it was on this neurological population that Schurch *et al*. (59) published their ground-breaking work in 2000, subsequently positioning botulinum toxin A in our therapeutic arsenal. The randomized phase 3 trial published by Cruz *et al.* in 2011 (60), which led to the first marketing authorization in France, reported a significant reduction in UUI episodes at 12 weeks post-injection, with an average of -20.5 episodes/week for onabotulinumtoxina 200U, versus -12.2 episodes/week

for placebo. This reduction in UUI episodes was associated with a significant improvement in urodynamic parameters, including an increase in maximum cystometric capacity (+157.0 mL, versus +6.5 mL) and a decrease in maximum detrusor pressure (-28.5 cmH_2 O, versus +6.4 cmH_2 0). In terms of safety, the urinary tract infection rate at 12 weeks was assessed at 27.5% for onabotulinumtoxina 200U, versus 22.2% in the placebo group. In addition, an episode of urinary retention was reported in 19.8% of patients in the 12 weeks following injection, versus 3.3% in the placebo group.

In 2019, onabotulinumtoxina 100U was granted an extension of its marketing authorization in France under the following heading: "urinary incontinence resistant to anticholinergics in patients with multiple sclerosis and a preserved spontaneous micturitions". The randomized phase 3 trial published by Tulllman *et al.* in 2018 (61), which led to the extension of this initial marketing authorization - and which only included MS patients not yet using CISC - reported a significant reduction in UUI episodes at 12 weeks post-injection, evaluated on average at -2.8 episodes/day for onabotulinumtoxina 100U, compared with -1.1 episodes/day for placebo. In terms of safety, the urinary tract infection rate at 12 weeks was 13.6% for onabotulinumtoxina 100U, versus 6.4% for placebo. In addition, an episode of urinary retention associated with the initiation of CISC was reported in 15.2% of patients within 12 weeks of injection. Although the frequency of MS patients requiring CISC after a first injection of onabotulinumtoxina 100U may seem high (15.2%), it should be contrasted with the even higher frequency of CISC use in this same population after a first injection of onabotulinumtoxina 200U (30.2%) (60).

More recently, in 2022, abobotulinumtoxina 600U and 800U received their first marketing authorization in France under the heading: *"Urinary incontinence in adults with neurological detrusor hyperactivity due to spinal cord injury (traumatic or non-traumatic) or multiple sclerosis, who regularly perform clean intermittent catheterization".* The randomized phase 3 trial published by Denys *et al.* in 2022 (62), which led to this first marketing authorization, reported similar results to those reported in 2011 with onabotulinumtoxina 200U, including a significant reduction in UUI episodes and a significant improvement in quality of life (I-QOL self-questionnaire) associated with a significant improvement in urodynamic parameters at 12 weeks from the first injection.

Regarding continuation of therapy, it appears to be more prolonged in the context of neurogenic OAB/UUI, with maintenance of injections at 5 years evaluated between 59.1 % and 81.1% (63,64).

Finally, it is important to note that onabotulinumtoxina and abobotulinumtoxina only have marketing authorization in France for two specific neurological populations: spinal cord injury and multiple sclerosis.

Sacral neuromodulation is an implantable device which received marketing authorization in France in 2002 for the treatment of neurogenic or non-neurogenic OAB/UUI, under the following heading: ″Disabling daytime frequency with or without urge urinary incontinence and disabling urgency, resistant to conservative treatments″. This therapy will be developed in greater detail in a dedicated section (Cf *IV. ELECTRICAL STIMULATION/MODULATION THERAPIES*).

Percutaneous tibial neurostimulation, considered a minimally invasive electrical stimulation therapy, is administered repeatedly in consultation by a healthcare professional. This therapy has not been developed in France, transcutaneous tibial neurostimulation having been preferred. Percutaneous tibial neurostimulation requires unilateral puncture of the tibial nerve and is therefore considered an invasive therapy in the same way as sacral neuromodulation. This is one of the reasons why it is often positioned as a third-line treatment in international recommendations (44). This therapy will be developed in greater detail in a dedicated section (Cf *IV. ELECTRICAL STIMULATION/MODULATION THERAPIES*).

III.1.d. Fourth-line treatments for neurogenic and non-neurogenic SCHV/IUU

The fourth line includes urinary tract reconstruction and/or diversion surgeries, and today concerns almost exclusively neurogenic OAB/UUI. These surgeries will not be specifically addressed here.

III.2. Algorithm for the management of voiding dysfunction

Clean intermittent self-catheterization (CISC) is considered the gold-standard in the context of neurogenic and non-neurogenic voiding dysfunction. However, certain validated alternatives - such as sacral neuromodulation - or non-validated ones - such as certain pharmacological approaches - can be proposed. In addition, bladder neck resection surgery can sometimes be performed in case of bladder neck obstruction. Urinary diversion surgery is considered a last resort, particularly in neurological patients.

III.2.a. Clean-intermittent self-catheterization: the gold-standard

Since the first publication by Lapides *et al.* in 1974 (65), CISC has gradually established itself as the gold-standard in the context of voiding dysfunction secondary to detrusor hypocontractility and/or functional bladder outlet obstruction, with no treatable cause (66). In fact, if hypocontractility is related to medication intake, adjusting the drug treatment, whenever feasible, should be considered as the first step. Similarly, if bladder outlet obstruction is the result of an anatomical obstruction (benign prostatic hyperplasia, urethral stricture), treatment of this obstruction should be proposed as the first step.

So, even if there is no universally accepted threshold in terms of maximal urinary flow or post-void residual, it is now recommended to initiate CISC whenever there is discomfort or complications (recurrent urinary tract infections, impact on the upper urinary tract) related to voiding dysfunction, and/or when there is a risk of complication, particularly on the upper urinary tract (66).

CISC involves the patient inserting a catheter into the bladder via the urethra, 5 to 6 times a day, to ensure regular, complete, low-pressure emptying of the bladder. This is considered a gold-standard, as it is the one which, in the context of voiding dysfunction, is more likely to limit complications of the lower and upper urinary tract than other modes of bladder management (indwelling urethral catheter, supra-pubic catheter, straining or even reflex micturition in spinal cord injury patients) (67). CISC also improves urinary symptoms and quality of life (68).

However, even though CISC is associated with an acceptable complication rate, and most patients are confident that it can be performed, many still feel embarrassed and express apprehension about potential long-term adverse effects (69). In this context, alternatives such as sacral neuromodulation may sometimes be proposed.

III.2.b. Sacral neuromodulation: a validated alternative

Sacral neuromodulation is an implantable device which received marketing authorization in France in 2002 for the treatment of neurogenic or non-neurogenic voiding dysfunction, under the following heading: *"Chronic urinary retention with striated sphincter hypertonia, with no detectable urological cause, resistant to conservative treatment".* This therapy will be developed in greater detail in the dedicated paragraph (Cf *IV. ELECTRICAL STIMULATION/MODULATION THERAPIES*).

III.2.c. Non-validated pharmacological alternatives

In the context of neurogenic and non-neurogenic voiding dysfunction, apart from anatomical obstruction causes (benign prostatic hypertrophy), drug alternatives have been studied. These include **alpha- blockers** (70), **phospho-di-esterase type 5 inhibitors** (Clara Fowler syndrome) (71) and **baclofen** (dysfunctional voiding in women) (72). Although some of these treatments have been shown to be beneficial in clinical practice, no well-conducted prospective randomized trial has demonstrated their efficacy.

Intra-sphincter injections of botulinum toxin A have also been studied in this context. In a review of the literature, Kao *et al* .(73) stated that - despite efficacy being reported in several retrospective and prospective non-randomized clinical trials - randomized clinical trials had only demonstrated an effect of these injections in the population of spinal cord injury patients. In this specific population, a significant improvement in symptoms was reported in 66% to 81% of cases, and the injections enabled spontaneous micturition to resume in 80% of cases, for a duration ranging from 2 to 6 months. It is important to remember, however, that botulinum toxin A has no marketing authorization in France for this indication.

III.2.d. Bladder neck resection surgery

In case of bladder neck obstruction, a bladder neck resection surgery - consisting of endoscopic resection of the bladder neck using a thermal loop or, more recently, a laser - may sometimes be discussed. In men, the results of bladder neck incision surgery have mainly been evaluated in the context of post-prostatectomy anastomotic stenosis. In women, in the context of primary bladder neck obstruction, several prospective non-comparative studies have reported a success rate of 91% to 100% in the short term (74–80), associated with a significant increase in maximal urinary flow and a significant reduction in post-void residual at short and medium term (76,80). On the other hand, it is important to note that all these studies reported a non-negligible rate of *de novo* stress urinary incontinence ranging from 3.3% to 9.1 % (74–80).

III.2.e. Urinary diversion surgeries

Urinary diversion surgeries, whether to create a continent cutaneous urinary diversion - enabling to perform CISC via the abdominal route - or to create a non-continent urinary diversion (ileal conduit), can be offered as a last resort, particularly in the neurological population. These surgeries will not be specifically addressed here.

IV. ELECTRICAL STIMULATION/MODULATION THERAPIES

First, we need to clarify the difference between neurostimulation and neuromodulation, two terms that are sometimes misused. Neurostimulation is defined as the stimulation of a nerve - whether by means of an electrical impulse or not. Neuromodulation is defined as the modification of nerve function - sometimes through neurostimulation, particularly electrical. So, for the sake of accuracy, the terms "tibial neurostimulation" and "sacral neuromodulation" - which reflect linguistic habits rather than a true understanding of the mechanisms of action of these two therapies - should probably be replaced by "neuromodulation via electrical tibial /sacral neurostimulation". For the sake of simplicity, and in keeping with the current usage of

these terms by the scientific community, we will continue to use the terms "tibial neurostimulation" and "sacral neuromodulation" in the remainder of this work.

Gamé and Phé, in the Report of the French Congress of Urology published in 2021 and focusing on OAB, have elegantly summarized the principles of neuromodulation as it is currently used in urology (81). According to them, *"the principle of neuromodulation is to regulate lower urinary tract function by modulating its innervation, in particular the micturition reflex, by stimulating peripheral innervation in various ways. Neuromodulation can be performed through transvaginal, transanal or transcutaneous approach; or invasively, either percutaneously or via an implantable device. The two forms of neuromodulation routinely used in France are based on stimulation of the tibial nerve or stimulation of a sacral root, particularly S3".*

IV.1. Tibial neurostimulation

IV.1.a. History of tibial neurostimulation

Tibial neurostimulation involves unilateral (rarely bilateral), intermittent electrical stimulation of the tibial nerve at the point described as SP6 in traditional Chinese medicine (82). Although this therapy, initially developed by Stoller in the 1980s (83), could be considered by some to be a form of electro-acupuncture, it was discovered in different circumstances. Stoller, investigating potential approaches to peripheral neuromodulation of the spinal cord, recorded multiple skin impedance measurements along the S2 and S3 dermatomes. He identified an area of high impedance above the medial malleolus, which later proved to correspond to the SP6 acupuncture point - traditionally targeted for the management of a variety of urinary disorders in traditional Chinese medicine (82). Since this discovery and following the first human trial by McGuire *et al.* in 1983 (84), numerous studies have demonstrated the efficacy and safety of tibial neurostimulation in various indications, notably for the management of OAB/UUI. Its use in urology has thus developed considerably over the last 20 years, particularly in France in its transcutaneous form.

IV.1.b. The different types of tibial neurostimulation

Today, tibial neurostimulation can be administered percutaneously or transcutaneously.

Percutaneous tibial neurostimulation involves direct stimulation of the tibial nerve using a needle inserted through the skin. Stimulation is administered in consultation by a healthcare professional on a weekly - or even bi-weekly - basis for 12 weeks. The default setting is a stimulation pulse rate of 20Hz and a pulse duration of 200µs. Stimulation can sometimes be repeated remotely if symptoms recur. This is the most widely used and studied route of administration worldwide, particularly in Western countries. However, it is not offered in France, where transcutaneous tibial neurostimulation has been more widely developed.

Transcutaneous tibial neurostimulation involves stimulating the tibial nerve through the skin using skin patches. Stimulation is self-administered on a daily basis, for 20 to 30 minutes a day, for 12 weeks. The default setting includes a stimulation pulse rate of 10Hz and a pulse duration of 200µs. Stimulation can be continued beyond this, and for longer periods, if it has significantly improved the patient's symptoms.

IV.1.c. Mechanisms of action of tibial neurostimulation

Since its discovery in the 1980s, numerous avenues have been explored to understand the mechanisms of action of tibial neurostimulation. Starting from the observation that the tibial nerve is a sensory-motor nerve emanating from L4-S3 contingents, the following have been successively evoked: increased pelvic blood flow (83), modification of the neurochemical environment along the sacral pathways (82), a "gate- control " effect (85) - particularly in the S3 root -, repeated activation of acute and/or chronic inhibitory reflexes involving the bladder (86), co-activation of the saphenous nerve (87), and an effect on cerebral structures (88). However, none of these hypotheses alone can explain the mode of action of tibial neurostimulation, which remains largely unknown to this day.

IV.1.d. Efficacy of tibial neurostimulation

In the non-neurogenic population, tibial neurostimulation significantly improves OAB in 48% to 93% of cases, and results in complete resolution of UUI in 25% to 45% of cases after 12 weeks of stimulation (89). A recent meta-analysis published in 2021 by Xiong *et al .(90)* even demonstrated a comparable efficacy of tibial neurostimulation when compared with anticholinergic treatments for 6 to 12 weeks - notably in terms of daytime frequency and urgency. Tibial neurostimulation even appeared to be more effective than anticholinergic treatments in terms of the PGI-I (Patient's Global Impression of Improvement) score.
Although most of the trials focused on percutaneous tibial neurostimulation - and more marginally transcutaneous tibial neurostimulation - it is worth mentioning the meta-analysis published by Yang *et al* .in 2021 (91). Indeed, after including 4 separate studies (142 patients), the authors reported similar efficacy of tibial neurostimulation whether administered percutaneously or transcutaneously - notably in terms of daytime frequency and urgency.

In the neurogenic population, tibial neurostimulation has been studied mainly in patients with MS or Parkinson's syndrome.
Kabay *et al*. (92) were the first to evaluate tibial neurostimulation in **MS** patients. In 2008, based on a retrospective study of 29 patients, the authors demonstrated that percutaneous tibial neurostimulation significantly improved urodynamic parameters, with an increase in maximum cystometric capacity (193.93 ± 9.90 mL *vs.* 286.48 ± 9.09 mL; p <0.001) associated with an increase in filling volume at first detrusor contraction (138.3 ± 6.4 mL *vs.* 230.5 ± 8.9 mL; p=0.001). Furthermore, in 2011, De Sèze *et al. (93)* presented the results of transcutaneous tibial neurostimulation in 70 MS patients. The authors reported a significant improvement in OAB in 82.6% and 83.3% of patients after 30 and 90 days of stimulation, respectively. In addition, they reported a urodynamic response - defined as an increase of >30% in maximum cystometric capacity - in 51.2% of cases. Since then, other studies have confirmed these results (94,95).

In patients with **Parkinson's syndrome,** the first study was published by Kabay *et al*. in 2009 (96). It involved 32 patients with idiopathic Parkinson's disease. The authors demonstrated that percutaneous tibial neurostimulation significantly improved urodynamic parameters,

with an increase in volume at first detrusor contraction (145.2 ± 41.1 mL vs. 244.7 ± 51.7 mL, p = 0.001), associated with an increase in maximum cystometric capacity. (204.8 mL ± 40.5 vs 301.2 ± 51.5 mL, p = 0.001). After 12 weeks of stimulation, the treatment was considered effective in 23/32 patients (71%).

In 2021, Araujo *et al. (97)* reported the first prospective randomized sham-controlled trial, including 30 women with Parkinson's syndrome (15 in each group). After 12 weeks of transcutaneous tibial neurostimulation, the authors reported a significant improvement in all symptoms related to OAB, including a reduction in the number of nocturia episodes (0.9 ± 0.6), the number of urgency episodes (1.0 ± 1.2), the number of UUI episodes (0.5 ± 0.6), associated with a reduction in the use of sanitary towels (1.3 ± 1.2). Interestingly, the authors reported that efficacy was maintained after 30 days and 90 days of cessation of stimulation, in 53.3% and 33.3% of cases, respectively.

More recently, in 2022, McClurg *et al.* (98) published a second randomized sham-controlled trial (STARTUP trial) involving 242 patients (121 in each group) with idiopathic Parkinson's disease. The authors reported a significantly lower IPSS score in the group receiving transcutaneous tibial neurostimulation for 6 weeks (10.9 ± 5.5 vs. 12.5 ± 6.5), with an estimated effect size of - 1.49,$_{95\%IC}$ (-2.72; -0.25). Bearing in mind that a 3-point difference in IPSS score is considered clinically significant, and that no other parameter was significantly improved, the results of this trial appear disappointing, to say the least.

Castel-Lacanal *et al.* in an unpublished (ongoing submission) randomized sham-controlled trial (UROPARKTENS trial), assessed the efficacy of transcutaneous tibial neurostimulation on lower urinary tract dysfunctions in 100 patients with Parkinson's syndrome (85 with idiopathic Parkinson's disease). After 12 weeks of treatment, 68 patients reported improvement (PGI-I: 1-3), including 30 patients (64%) in the transcutaneous tibial neurostimulation group and 38 patients (71%) in the "sham" group. There was no statistically significant difference between the 2 groups for any parameter. To explain the importance of the placebo effect, the authors point out that the magnitude of the placebo effect depends on many factors, including the underlying pathology. The placebo effect has been shown to be particularly important in idiopathic Parkinson's disease, with a placebo response obtained in over 50% of patients (99). This effect appears to be even more pronounced in the case of invasive treatment or advanced disease, and correlates with dopaminergic activation in the striatum (100). Therefore, in the

authors' view, the high level of the placebo effect could probably be related to the population studied.

Thus, while the efficacy of percutaneous or transcutaneous tibial neurostimulation in the management of non-neurogenic OAB/UUI has been reported in numerous trials, the same cannot be said for neurogenic OAB/UUI. In MS, although several retrospective trials have reported interesting results - whether in terms of symptoms or urodynamic improvement - only one randomized trial has been conducted to date (95). In the context of Parkinson's syndrome, despite having three randomized trials, the results are generally disappointing, with a significant placebo effect often observed.

IV.1.e. Safety of tibial neurostimulation

The safety of tibial neurostimulation is generally very good, with very few side effects, although these may include discomfort or pain associated with stimulation, and exceptionally a hematoma at the puncture site for the percutaneous approach (81).

IV.1.f. Tibial neurostimulation outside of OAB/UUI

Tibial neurostimulation appears to have effects beyond OAB/UUI, and even beyond the lower urinary tract. It is therefore now possible to consider its place in the management of other pelvic floor dysfunction, including voiding dysfunction, as well as refractory constipation.

Thus, in a review of the literature published in 2015, Schneider *et al. (101)* demonstrated, from 5/16 studies that evaluated bladder emptying before and after administration of tibial neurostimulation, that post-void residual decreased on average 16 mL to 55 mL. Although this may seem a marginal improvement, it is important to note that, unlike other therapies - such as anticholinergic treatments or botulinum toxin A - tibial neurostimulation does not appear to have an adverse impact on bladder emptying. Other results from studies of MS patients even suggest that tibial neurostimulation could be a potential treatment for voiding dysfunction. Kabay *et al. (102), in* a cohort of 19 patients who underwent tibial

neurostimulation, reported an increase in maximum urinary flow from 11.6 mL/sec (7-15) to 13.2 mL/sec (7-22) (p=0.003) and a decrease in post-void residual from 82.9 mL (0-276) to 48 mL (0-107) (p=0.006). In this cohort, 5 patients had detrusor-sphincter dyssynergia at inclusion. At the end of the study, 3 (60%) were free of detrusor-sphincter dyssynergia. In a second study by Gobbi *et al*. (94) involving 18 patients, tibial neurostimulation reduced the post-void residual from 98 mL (± 124) to 43 mL (± 45) (p = 0.02).

Concerning the management of refractory constipation, Pauwels *et al.* (103), reported in a review of the literature published in 2021 that tibial neurostimulation significantly improved defecation in 26% to 47% of patients.

IV.1.g. Limitations and prospects for tibial neurostimulation

We can agree that tibial neurostimulation - whether transcutaneous or percutaneous - should be further evaluated, particularly in the context of neurogenic OAB/UUI. However, in view of the efficacy already reported in non-neurogenic OAB/UUI, its safety profile and its potential effect on other pelvic floor dysfunctions, it is today a therapy of choice in the management of OAB/UUI and could even be considered tomorrow as an alternative in the management of certain types of voiding dysfunction.

It seems important that further research be carried out to advance our understanding of the mechanisms of action, to better position this therapy in our algorithms, optimize stimulation setting and protocols, and ultimately improve its efficacy.
It could also be interesting to assess the stimulation pulse rate and its impact in terms of efficacy and safety. Indeed, besides the approach and frequency of stimulation sessions, it is also the pulse rate that distinguishes transcutaneous tibial neurostimulation (10 Hz) from percutaneous tibial neurostimulation (20 Hz).
It should also be remembered that tibial neurostimulation, like other treatments already presented, is rarely continued over the long term. Thus, Leroux *et al.* (104) evaluated the 2-year continuation of transcutaneous tibial neurostimulation in 97 patients with non-neurogenic OAB/UUI. The authors reported a discontinuation rate of 71% and 84% respectively at 12 and 18 months after initiation. Constraint in the daily use of the device was

the main reason for discontinuation of the therapy between 12 and 18 months. In clinical practice, this constraint seems to be a major obstacle to the continuation of therapy over time, due to outdated and less ergonomic devices. New, more ergonomic, and easier-to-use devices are now emerging. Some of these devices are directly inspired by transcutaneous tibial neurostimulation (105,106), while others propose percutaneous approaches - with the need to first implant a subcutaneous electrode to enable self-administration of therapy at home via an external device (107). In parallel, some fully implantable tibial neuromodulation devices are under development and should be available in the next years (108).

IV.2. Sacral neuromodulation

IV.2.a. History of sacral neuromodulation

In 1878, Saxtorph was the first to describe an electrical stimulation technique for the management of patients with neurogenic voiding dysfunction (109). These therapies remained largely confidential or anecdotal throughout the 20th century, although a few scientific articles were published in the 1960-70s (110,111).
In 1971, Nashold *et al*. (112) set out to study these electrical stimulation therapies, attempting to implant a prosthesis in the sacral segment of the spinal cord in a patient with a history of spinal cord injury. The prosthesis was subsequently improved by Jonas and Tanagho (113), enabling Tanagho and Schmidt (114) to demonstrate in a 1988 that stimulation of the S3 sacral roots can modulate detrusor and sphincter activity.

In France, the first sacral neuromodulation device was implanted in 1995, and received marketing authorization in 2002 for the treatment of OAB/UUI, under the heading: "Disabling daytime frequency with or without urge urinary incontinence and disabling urgency, resistant to conservative treatments". Sacral neuromodulation also received marketing authorization in 2002 for the treatment of voiding dysfunction, under the heading: "Chronic urinary retention with striated sphincter hypertonia with no detectable urological cause, resistant to conservative treatments".

IV.2.b. Various sacral neuromodulation devices

All currently available sacral neuromodulation devices are designed in the same way. They comprise a quadripolar electrode connected to an internal generator. An external remote control communicates with the generator to modify stimulation parameters on demand.

Since 2020, two manufacturers have been positioned on the international market: Medtronic (Minneapolis, MN, USA) and Axonics Modulation Technologies (Irvine, CA, USA). In 2024, only Medtronic has obtained reimbursement for its therapy in France and is therefore currently the only manufacturer present on the French market.

Medtronic offers three distinct generators:

- The Interstim II generator (model 3058), available since 2009, is equipped with a lithium battery with an estimated lifespan of 5 to 7 years.
- The Interstim micro generator (model 97810), available since 2020, is smaller (2.8 cm^3 *vs* 12.5 cm^3) and rechargeable, with an estimated lifespan of 15 years. However, this generator needs to be recharged weekly (20-30 minutes) by induction using a dedicated external device.
- The Interstim X generator, not yet available in France, is equipped with a latest-generation lithium battery with an estimated lifespan of 10 years.

Since 2020, improvements to the quadripolar electrode (model 978B1 for the Interstim II generator, model 978A1 for the Interstim Micro generator) have made these three MRI devices compatible (3 Tesla, whole body). This MRI compatibility makes it possible to envisage the deployment of sacral neuromodulation in populations previously "deprived" of it, notably in patients with MS or deep pelvic endometriosis - who are regularly subjected to brain, spinal cord and/or abdominal MRI assessments.

In practice, sacral neuromodulation is implanted following a two-stage surgical procedure.
In the first stage, performed under general or local anesthesia, the sacral neuromodulation lead is implanted percutaneously and under fluoroscopic control, in contact with one of the two S3 sacral roots - more rarely S4. Correct positioning of the lead is verified by looking for

the presence of a motor response corresponding to stimulation of the S3 sacral root - i.e. contraction of the anus associated with contraction of the homolateral hallux. At the end of the procedure, the electrode is connected to an external generator. This is followed by a test phase lasting from 2 to 4 weeks, during which several stimulation programs can be tested, and their clinical and urodynamic efficacy assessed. By consensus, the therapy is deemed effective if it demonstrates an improvement of at least 50% in the patient's bothersome urinary symptoms. If the test phase is successful, an internal implantable pulse generator (IPG) is connected to the lead in a subcutaneous (often supra-gluteal) position during the second stage - often performed under local anesthesia. If the test phase is unsuccessful, the lead is removed during this second stage.

The electrical stimulation delivered at the lead is an intermittent rectangular current. Stimulation parameters therefore include polarity (i.e. the contact point from which the current is delivered), stimulation pulse rate (Hz), stimulation pulse duration (µs) and stimulation intensity (mA). Only the stimulation intensity can be modified by the patient. The other parameters can be modified by the therapist in charge of setting up sacral neuromodulation. Default stimulation parameters include a pulse rate of 14Hz and a pulse duration of 210 µs. Polarity setting is left to the therapist's discretion, who can use one or more of the 7 default polarities - theoretically covering all possibilities - or propose a customized polarity considering intra-operative motor and sensory response.

While the technique for implanting the sacral neuromodulation lead is now well standardized (115) , the setting strategy has not yet been the subject of any consensus (116).

IV.2.c. Mechanisms of action of sacral neuromodulation

Our understanding of the mechanisms of action of sacral neuromodulation is still largely incomplete. However, we can state that electrical stimulation of the sacral root generates an action potential that propagates along the axon, activating somatic afferent nerves and inhibiting bladder and/or urethral sensory pathways (117). Thus, unlike other therapies that directly target the lower urinary tract, it seems that sacral neuromodulation acts on afferent pathways and medullary and supramedullary structures. Moreover, the maximum effect of

nerve stimulation is often only reached in a delayed manner, after prolonged stimulation, suggesting that nerve stimulation induces adaptive changes (neuronal plasticity) at medullary and/or cerebral level (118). In addition, Gill *et al.* (24) have shown, based on a brain fMRI study, that the intensity of stimulation can modify the mechanism of action of sacral neuromodulation. Indeed, the authors demonstrated that the pattern of brain activation differed according to the intensity of stimulation applied. Thus, for **sub-sensory stimulation** (below the sensitivity threshold), they reported deactivation of the PMC and PAG, indicating inhibition of the micturition reflex. For **sensory stimuli** (at the level of the sensitivity threshold), they reported activation of the insula, involved in the Salience Network and modulating the interaction of the prefrontal cortex with the PAG, the activity of the thalamus and, indirectly, the sympathetic activity directed towards the lower urinary tract. For the authors, these changes could be explained in two distinct ways. They could be the result of a cascade of changes through the prefrontal cortex, the PAG and the PMC - in which, activation of the PAG could suggest the re-establishment of a "continence reflex". This increase in insula activity could also increase thalamic activity and indirectly participate in an increase in lower urinary tract sympathetic tone, thus promoting bladder relaxation and contraction of the sphincteric complex. For **supra-sensory stimulation** (above the threshold of sensitivity), the authors reported activation of several structures including the thalamus and the posterior cingulate cortex, suggesting that supra-sensory stimulation bypassed some of the normal pathways involved in regulating the micturition cycle, perhaps exerting effects via a "flight or fight" influence on sensation and function of the lower urinary tract.
However, in addition to an effect on afferents, some authors have demonstrated that sacral neuromodulation may also have a direct effect on efferent nerves. Indeed, Vaganée *et al. (119)* recently demonstrated that the pelvic floor contraction observed during intense sacral root stimulation is unlikely to be secondary to an afferent-mediated medullary reflex, but rather to direct afferent stimulation of pelvic floor muscles.

It is important to note that all these studies evaluated the mechanism of action of sacral neuromodulation using mostly default settings (14Hz, 210 µs), without ever specifying the polarity setting. However, a few studies have demonstrated that modifying these default settings - whether in pulse rate (120) or in pulse duration (121) - can improve the efficacy of sacral neuromodulation.

IV.2.d. Efficacy of sacral neuromodulation

In the context of non-neurogenic OAB/UUI, the randomized INSITE trial versus conventional drug treatment (anticholinergics) published by Noblett *et al*. in 2016 (122) reported a success rate of the test phase of 61% on intention to treat (versus 42% for drug treatment; p = 0.02) and 76% in patients actually treated (versus 49% for drug treatment; p = 0.002). In addition, 5-year follow-up showed that the efficacy of sacral neuromodulation was maintained in 82% of cases.

These results were confirmed by the SOUNDS trial published in 2021 (123). This prospective observational French trial conducted by Chartier-Kastler *et al*. included 301 patients, 78% of whom underwent primary implantation and 22% a change of IPG. Like the INSITE trial, the efficacy criterion was defined as "an improvement of > 50% in the number of daily UUI episodes and/or the number of daily micturitions compared with the reference measurement, or a return to normal daily frequency (<8 daily micturitions)". At 3 months to the test phase, 78% of primary implant patients and 71% of patients who had undergone an IPG change were significantly improved. At 5 years, efficacy maintained in 68% of primary implant patients and 61% of patients who had undergone an IPG change.

Although these results may appear satisfactory, two major limitations need to be highlighted: the rate of "cured" patients, as well as “real life” long-term follow-up and efficacy. Regarding the rate of patients who are truly "cured", among patients with UUI at the time of the test phase, only 25% to 36% regained full continence at 3 months, and among these patients, only 33% to 45% were still continent at 5 years (124). So, even though sacral neuromodulation appears to be the only therapy that can be maintained over time - compared to all other second- and third-line therapies - the fact remains that it only "cures" a minority of patients. As for long-term follow-up, although it may appear satisfactory in prospective controlled trials, several prospective and retrospective “real-life” studies have systematically reported a decrease in the efficacy of sacral neuromodulation over time. Thus, Hernandez-Hernandez *et al .(125)* and Janssen *et al.* (126) reported a loss of efficacy of the therapy in 28.5% and 32.0% of cases, after 61.4 months and 85.0 months of follow-up, respectively. Similarly, Elhilali *et al.* (127) reported maintenance of efficacy in only 45.0% of patients 3 years after IPG implantation. These losses in efficacy may necessitate a change in settings, surgical revision or the addition or change of another treatment.

The prospective randomized ROSETTA trial (128) compared sacral neuromodulation with botulinum toxin A in the context of non-neurogenic OAB/UUI. Of the 386 patients included, 192 received iterative intravesical injections of onabotulinumtoxina 200U, and 194 had a sacral neuromodulation test. In terms of efficacy, results were similar after 2 years of follow-up, particularly concerning the primary endpoint, the number of daily UUI episodes. In terms of safety, the urinary tract infection rate was 3 times higher in the group receiving iterative injections of botulinum toxin A, and 20% of patients had to perform CISC within the first 6 months. It is important to remember that onabotulinumtoxina is approved in France for this indication at doses of 50U and 100U. Results of the ROSETTA trial are therefore difficult to extrapolate to our daily clinical practice, in terms of efficacy and side effects.

In the context of neurogenic OAB/UUI, sacral neuromodulation has been evaluated in numerous neurological populations as evidenced by the meta-analysis published by van Ophoven *et al.* in 2021 *(129).* Twenty-one studies involving a total of 887 patients were included to assess the success of the test phase. The overall success rate of the test phase was 66.2% ($_{95\%CI}$[56.9; 74.4]), although there was considerable variation depending on the underlying neurological population. So, as Panicker *et al. (13)* reminded us in 2015, we have yet to clarify which neurological patients are most likely to benefit from sacral neuromodulation.

Sacral neuromodulation has been studied specifically in MS patients. Since the first study reported by Minardi and Muzzonigro in 2005 (130), several retrospective studies have confirmed the interesting results of sacral neuromodulation, with success rates of the test phase ranging from 53.3% to 94.0% (131,132). The largest cohort, published in 2012 by Minardi and Muzzonigro (132) and including 25 patients, reported a test-phase success rate of 60.0%. The arrival in 2020 of MRI-compatible devices and the promising results of sacral neuromodulation in this specific population should encourage us to better evaluate it, particularly in terms of medium- and long-term efficacy and urodynamic effectiveness - which remains a major issue in patients with underlying neurological pathology, sometimes with lower urinary tract dysfunctions at risk for the upper urinary tract.

In the context of voiding dysfunction, the data are more challenging to interpret, notably because the studied populations are heterogeneous and that there is not yet a clear consensus

on the definition of success. Nevertheless, it can be said that sacral neuromodulation significantly improves bladder emptying in 33% to 100% of cases, with a median follow-up ranging from 6 to 60 months (133,134).

These relatively heterogeneous results inevitably lead us to question the existence of predictive factors for the success of sacral neuromodulation - whether clinical or urodynamic - in the context of voiding dysfunction, but also in the context of OAB/UUI.

A recent review of the literature published by Jairam *et al.* (135) in 2022 highlighted several predictive factors for success with sacral neuromodulation, whether in the context of OAB/UUI or voiding dysfunction. Although some predictive factors have been reported by numerous authors - suggesting that they could be used in clinical practice to support the shared decision making process - no predictive tools have yet been developed for such a use.

IV.2.e. Safety of sacral neuromodulation

Although sacral neuromodulation is generally well tolerated, it is associated with a number of complications. For example, in the INSITE trial (136), 30% of patients reported a therapy-related side effect during the 5-year follow-up period, 56% of which occurred within the first 3 months after IPG implantation. Complications included stimulation-related discomfort in 12% of cases, pain at the implantation site in 7% of cases - requiring repeat surgery in 50% of cases, and surgical site infection in 3% of cases requiring removal of the device.
These data were confirmed by other studies, in which the authors reported a rate of complications or side effects ranging from 30.0% to 42.0% during an average follow-up of 6 to 24 months (123,137–140). These complications could require revision surgery in almost a third of patients (137).

IV.2.f. Sacral neuromodulation outside lower urinary tract dysfunctions

Sacral neuromodulation appears to have effects beyond the lower urinary tract. In 2009, it was granted marketing authorization for the treatment of fecal incontinence, under the heading: "Fecal incontinence resistant to conservative treatment, with a functional anal sphincter".

In addition, it seems that sacral neuromodulation could be proposed in certain types of constipation, as evidenced by the results of a literature review published by Heemskerk *et al*. in 2024 (141).

Sacral neuromodulation is also sometimes proposed for the management of chronic pelvic pain syndrome. In a review of the literature published in 2023, Greig *et al.* (142) included 26 articles involving 853 patients. They reported a success rate of 64.3%, a significant reduction in pain-related scores in 13 studies, and a significant improvement in quality of life in all studies.

IV.2.g. Limits and prospects of sacral neuromodulation

Overall, sacral neuromodulation is an effective therapy for the management of neurogenic and non-neurogenic OAB/UUI, as well as for the management of certain types of voiding dysfunction, and more generally, for the management of pelvic floor dysfunctions. However, we have yet to define in which population and with which clinical and/or urodynamic picture(s) sacral neuromodulation could be most effective.

Moreover, it seems that sacral neuromodulation is the only second- or third-line therapy that can be maintained over the medium or long term, at the cost of regular follow-up, which may involve adjusting the stimulation settings, revising the IPG and/or lead, or even adding or modifying certain concomitant treatments.

We also believe it is important to continue research to better understand the mechanisms of action, as well as the stimulation settings strategy - which, although often proposed using default parameters, is still far from being consensual.

V. ELECTRICAL STIMULATION/MODULATION THERAPIES AND THEIR IMPACT ON THE CENTRAL NERVOUS SYSTEM AND THE AUTONOMIC NERVOUS SYSTEM

V.1. Tibial neurostimulation

V.1.a. Tibial neurostimulation and the activity of brain structures

Krhut *et al. (143)* evaluated acute changes in brain activity in response to different types of electrical stimulation, including tibial stimulation, peroneal stimulation, and "sham" stimulation. For this study, 32 "healthy" women were included, and brain fMRI (3 Tesla) was performed comprising three 8-minute blocks of alternating sequences. During each 8-minute block, the protocol alternated between "sham" stimulation (30s) and a rest period (30s) for 8 repetitions; then peroneal stimulation (30s) and a rest period (30s) for 8 repetitions; finally, tibial stimulation (30s) and a rest period (30s) for 8 repetitions. The authors reported activation of the left cerebellum, right transverse temporal gyrus, right middle frontal gyrus and right inferior frontal gyrus only during peroneal and tibial stimulation. They also reported activation of the right cerebellum, right thalamus, bilateral basal ganglia, bilateral cingulate gyrus, right anterior insula, right central operculum, bilateral supplementary motor cortex, bilateral superior temporal gyrus and left inferior frontal gyrus during peroneal stimulation. These results indicate a probable effect of tibial neurostimulation at the central level, with the possibility of modifying cerebral activation areas. Interpretation is limited, however, by the fact that the study population consisted exclusively of "healthy" subjects, preventing any attempt to correlate the observed changes in brain activity with a clinical effect of the therapy.

V.1.b. Tibial neurostimulation and brain connectivity

Wöllner *et al.* (144) evaluated functional brain connectivity using fMRI (3 Tesla) in 14 "healthy" patients before and after application of transcutaneous tibial neurostimulation. The authors reported an increase in functional brain connectivity between the inferior frontal gyrus, posterior cingulate gyrus and middle temporal gyrus, with the precuneus being the central receptor. The authors also reported reduced connectivity in the cerebellum, hippocampus and

parahippocampal areas. These results point to a probable effect of tibial neurostimulation at the central level, with the possibility of modifying functional cerebral connectivity. Here again, interpretation is limited by the study population, which consisted solely of "healthy" subjects, preventing any attempt to correlate the observed changes in functional brain connectivity with a clinical effect of therapy.

V.1.c. Tibial neurostimulation and the autonomic nervous system

Stampas *et al. (145)* conducted a pilot randomized sham-controlled trial (2:1) including 16 patients with recent SCI (< 1 month). Patients received transcutaneous tibial neurostimulation with a daily 30-minute session for 2 weeks. Urodynamic assessment and concomitant evaluation of ANS activity by HRV measurement were performed before and 2 weeks after initiation of transcutaneous tibial neurostimulation. Urodynamically, maximum detrusor pressure was significantly increased in "sham" patients (48 cmH_2O *vs* 33 cmH_2O; p=0.04). This was not the case in patients receiving transcutaneous tibial neurostimulation (42 cmH_2O *vs* 34 cmH_2O; p=0.11). In terms of ANS activity, the authors reported a decrease in SNS activity during bladder filling in patients receiving transcutaneous tibial neurostimulation; and an increase in PSNS activity in "sham" patients. However, these results must be interpreted cautiously, not only due to the small number of included patients - which could potentially increase the risk of type II statistical error (β-error) - but also because 11 out of 16 patients are described as having complete spinal cord injury (AIS A) at inclusion.

V.2. Sacral neuromodulation

V.2.a. Sacral neuromodulation and the activity of brain structures

Weissbart *et al.* (146) studied changes in the activity of sacral neuromodulation-related brain structures, before and after sacral nerve stimulation, using brain fMRI (3 Tesla) in women with OAB/UUI. In this study, the neuromodulator was switched off immediately before imaging and urgency was induced by artificial bladder filling. In women who responded to sacral neuromodulation, a decrease in the activation of structures usually associated with urgency was reported. More specifically, brain activity decreased in the cingulate cortex, insula and

frontal cortex. At the same time, no new areas of increased activation were identified. Interestingly, the authors also identified a specific fMRI phenotype in the responders. For example, women who responded to sacral neuromodulation showed greater brain activity in the cingulate cortex, insula and frontal cortex, as well as in the SMA and sensory-motor cortex, prior to the intervention, compared with patients who did not respond to the therapy.

As we have already reported, Gill *et al*. (24) demonstrated that changes in brain activity associated with sacral neuromodulation in women with OAB/UUI depended on the intensity of stimulation delivered. The authors kept the neuromodulator on during imaging and used the change in delivered stimulation intensity as a study task. At subthreshold stimulation, the authors reported PMC and PAG deactivation. When stimulated at threshold, the authors reported activation of the insula, while when stimulated above threshold, the authors reported activation of the thalamus.

Kavia *et al*. (147) evaluated changes in brain structure activity before and after sacral neuromodulation implantation in 6 women with Clara Fowler syndrome. The authors reported abnormal deactivation of the right insula at the onset of bladder filling. This deactivation tended to normalize after implantation of sacral neuromodulation, suggesting that sacral neuromodulation could block inhibition of urethral afferents, with a visible effect on the activity of brain structures.

V.4.b. Sacral neuromodulation and brain connectivity

To our knowledge, no study has evaluated the effect of sacral neuromodulation on cerebral connectivity. However, Netto *et al*. (148) evaluated the effect of transcutaneous sacral neurostimulation on functional brain connectivity, using fMRI (3 Tesla). The authors included 10 "healthy" patients (5 men and 5 women) and performed a functional brain MRI acquisition comprising 3 distinct times: at rest, during transcutaneous sacral neurostimulation (10Hz, 260 µs), and during scapular sacral neurostimulation - control (10Hz, 260 µs). In all three situations, the authors reported strong connectivity between the ACC and subcortical regions, and between the ACC and the frontal lobe. In contrast, they reported an increase in functional

connectivity between the ACC and the dorsal lateral prefrontal cortex only during the time of transcutaneous sacral neurostimulation.

V.2.c. Sacral neuromodulation and the autonomic nervous system

To our knowledge, no study has evaluated the effect of sacral neuromodulation on ANS activity.

VI. OBJECTIVES OF THE THESIS

Whether in the context of OAB/UUI or certain types of voiding dysfunctions, we must admit that our diagnostic approaches still struggle to encompass the multiplicity of underlying etiopathogenesis, and that our rigid and vertical therapeutic algorithms imperfectly address the heterogeneity of pathological situations.

Even though it corresponds to the alternation between a bladder filling phase and a bladder emptying phase, the normal micturition cycle cannot be summed up as a binary operation but involves the constant consideration of multiple factors: the filling level of the bladder reservoir, the safety of the environment in which live, the emotional context in which we evolve and the social constraints to which we are subjected.

Recent advances and interest in brain imaging and the study of the ANS - as a regulatory interface - have led to a better understanding of how brain structures organize and interact with each other in complex and plastic networks to regulate lower urinary tract function, both in pathological and non-pathological situations.

We now have an overview of the alterations and/or modifications in brain activity and connectivity, as well as changes in ANS regulation, observed in certain types of lower urinary tract dysfunctions - notably in some OAB/UUI and certain types of voiding dysfunctions.

Among the therapies available today, electrical modulation/stimulation therapies (tibial neurostimulation and sacral neuromodulation) appear able of normalizing and/or modifying

cerebral activity and connectivity, as well as ANS balance. They could thus provide at least a partial response to some of the etiopathogenies underlying these lower urinary tract dysfunctions.

These electrical modulation/stimulation therapies also have an interesting efficacy and tolerance profile. Thus, in the context of OAB/UUI, tibial neurostimulation offers similar or even superior efficacy to first-line drug treatments, is associated with a particularly good tolerance profile, and could help improve a number of other associated pelvic floor dysfunction (voiding dysfunction, constipation).
Similarly, sacral neuromodulation appears to be as effective as botulinum toxin A, with a clear superiority in terms of medium- and long-term continuation of treatment. Sacral neuromodulation may also improve several other pelvic floor dysfunctions (voiding dysfunction, anal incontinence, constipation, chronic pelvic pain). It is also the only reversible therapy currently validated as an alternative to CISC for voiding dysfunction.

However, the deployment and positioning of these electrical modulation/stimulation therapies are still limited by:

Incomplete understanding of their mechanisms of action

To date, studies exploring the mechanisms of action of electrical modulation/stimulation therapies have mainly focused on sacral neuromodulation (149). However, although it seems certain that sacral neuromodulation can act via afferences and influence the activity and connectivity of supramedullary structures, no study has questioned its effect on the balance of the ANS - considered to be the regulatory interface between cerebral structures and the lower urinary tract (2). In addition, some teams have recently demonstrated, rather disruptively, that sacral neuromodulation could also act via the efferences (119).
Furthermore, as they are electrical stimulations/modulations involving the same territories - S3 for sacral neuromodulation; L4-S3 for tibial neurostimulation - we might be tempted to understand them as therapies sharing the same mechanism of action. However, this is not what the few exploratory studies evaluating the correlation in efficacy between tibial neurostimulation and sacral neuromodulation seem to tell us (150,151).

Imperfect identification of the indications and populations most likely to benefit from these therapies

In fact, although several factors have been proposed to predict success - whether in the context of OAB/UUI or voiding dysfunction (135) - no predictive tools that can be used in current clinical practice have yet been developed.

In addition, the advent of compatible MRI devices (3 Tesla, whole-body) - 2020 in France - raises the possibility of offering this therapy to certain neurological populations, notably MS. However, data on efficacy and safety in these populations are still sparse. Furthermore, in neurological populations, particularly those suffering from MS, it is important to remember that the management of lower urinary tract dysfunctions need to consider the uro-nephrological risk, and in particular detrusor pressures. However, while the clinical efficacy of tibial neurostimulation and sacral neuromodulation has been regularly evaluated, the same cannot be said of their urodynamic efficacy.

Finally, the idea that these electrical stimulation/modulation therapies can promote neuroplasticity processes is beginning to emerge (33), perhaps opening the way to new indications in the prevention of certain lower urinary tract dysfunctions, particularly in the early phase of spinal cord injury.

A lack of consensus on the setting of the electric current delivered

Although the technique for implanting the sacral neuromodulation lead has been the subject of a consensus (115), it seems necessary to recall that the adjustment strategy has not yet been the subject of any consensus (116) . Thus, the electric current delivered by the lead is currently set by default (14Hz, 210 µs) at an intensity that is often sub-sensory. However, a number of exploratory studies suggest that other setting strategies, such as pulse rate (152,153) or pulse duration (120), could in certain situations provide more effective therapy. In addition, the fMRI study reported by Gill *et al.* (24) suggests that stimulation intensity may also modify the mode of action and perhaps the efficacy of therapy.

It is also worth remembering that although transcutaneous tibial neurostimulation (10Hz, 200µs) and percutaneous tibial neurostimulation (20Hz, 200 µs) appear to have similar efficacy profiles (91), the stimulation settings used are not comparable. Should we therefore

simplify this finding by reducing it to the lack of impact of pulse rate on therapy efficacy, or should we rather consider it as a new field of investigation? Indeed, in concluding that these two therapies had comparable efficacy, Yang *et al.* did not conclude that these two therapies improved OAB/UUI in the same patients (91) - in the sense of the same underlying etiopathogenies. To our knowledge, this question has not yet been addressed in the scientific literature.

A lack of medium- and long-term evaluation, particularly after definitive implantation of sacral neuromodulation

Despite efficacy appears to be maintained over time in prospective controlled trials, "real-life" studies report a decrease in the efficacy of sacral neuromodulation between 20% to 55% at 3 years (125–127). This loss of efficacy may necessitate a modification of the settings, a surgical revision or even the addition or change of another treatment. It would therefore be interesting to evaluate not only the maintenance of efficacy over time, but also the patient pathways after definitive implantation.
In addition, the new generations of transcutaneous tibial neurostimulators, because they are more ergonomic, should improve the rate of continuation of therapy in the medium to long term (105,106). This hypothesis has yet to be verified.

It therefore seems possible to optimize electrical stimulation/modulation therapies in the management of neurogenic and non-neurogenic lower urinary tract dysfunctions, focusing particularly on the following points (117):

Focus 1: Identifying the indications and populations most likely to benefit, by:

- Evaluating the short, medium and long-term clinical and urodynamic efficacy of tibial neurostimulation and sacral neuromodulation in specific neurological and non-neurological populations as a treatment for OAB/UUI and voiding dysfunction.
- Evaluating the short, medium and long-term clinical and urodynamic efficacy of tibial neurostimulation as a treatment for voiding dysfunction in neurological and non-neurological populations.

- Developing predictive tools for the success of tibial neurostimulation and sacral neuromodulation as treatments for OAB/UUI and voiding dysfunction.
- Evaluating the efficacy of tibial neurostimulation and sacral neuromodulation as preventive treatments in specific indications, in relation to their probable effect on neuroplasticity.

Focus 2: Clarifying acute and chronic mechanism(s) of action, particularly at the level of the central nervous system and autonomic nervous system, by:

- Confirming and refining results relating to changes in brain activity and connectivity - in the short, medium and long-term - related to tibial neurostimulation and sacral neuromodulation, as a treatment for OAB/UUI and voiding dysfunction.
- Evaluating changes in ANS activity related to tibial neurostimulation and sacral neuromodulation - in the short, medium and long-term - as a treatment for OAB/UUI and voiding dysfunction.

Focus 3: Specifying setting strategy - at baseline and in the event of loss of efficacy, by:

- Evaluating different initial setting strategies (pulse rate, pulse duration, intensity, polarity, cycling) on efficacy, safety, and battery life, for sacral neuromodulation, as a treatment for OAB/UUI and voiding dysfunction.
- Evaluating different setting strategies in the event of loss of efficacy (pulse rate, pulse duration, intensity, polarity, cycling) for sacral neuromodulation, as a treatment for OAB/UUI and voiding dysfunction.
- Evaluating different initial setting strategies (pulse rate, pulse duration, intensity, stimulation duration, stimulation period) on efficacy for tibial neurostimulation, as a treatment for as a treatment for OAB/UUI and voiding dysfunction.
- Evaluating different closed-loop conditional control strategies through afferent nerve activity analysis and autonomic nervous system analysis.

Focus 4: Improving patient follow-up and promoting treatment adherence, by:

- Investigating factors influencing patient adherence to treatment, such as ease of use of devices, management of side effects and overall patient satisfaction.
- Evaluating existing care pathways for patients receiving electrical stimulation/modulation therapies and identifying critical points where improvements could be made.
- Designing and evaluating interventions to improve adherence to follow-up, including educational programs, remote follow-up tools and psychosocial support strategies.

In the present thesis, we propose to address some of these objectives in 3 parts:

- Part I: Before therapy initiation, Questioning the indication
- Part II: At therapy initiation, Questioning the mechanisms of action
- Part III: After therapy initiation, Questioning the follow-up

PART I

BEFORE THERAPY INITIATION,

QUESTIONING THE INDICATION

EARLY INTERVENTIONS TO PREVENT LOWER URINARY TRACT DYSFUNCTION AFTER SPINAL CORD INJURY: A SYSTEMATIC REVIEW

To begin with, we questioned the role of electrical stimulation/modulation therapies as preventive approaches.

Indeed, these therapies are currently only used as symptomatic treatments, and are therefore only initiated once lower urinary tract dysfunctions have been observed. However, in the situation of the spinal cord injury patient, where lower urinary tract dysfunction is almost systematic, in connection with the emergence of a spinal cord automatism, a preventive approach could probably have its place, to delay or reduce the intensity of lower urinary tract dysfunction.

Electrical stimulation/modulation therapies, because they could promote neuronal plasticity, seem to meet this challenge.

The review presented below was published in the journal *Spinal Cord* in 2022 (154).

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ABSTRACT

Guidance for reporting: The present systematic review is reported according to the PRISMA guidelines.

Objectives: To synthetize the available scientific literature focusing on early interventions to prevent neurogenic lower urinary tract dysfunction (NLUTD) after acute supra-sacral spinal cord injury (SCI).

Methods: The review identified articles published through April 2021 in the PubMed, Embase, ScienceDirect and Scopus databases with terms regarding early interventions to prevent NLUTD after SCI. Abstract and full-text screenings were performed by three reviewers independently, while two reviewers performed data extraction independently. An article was considered relevant to this literature review if it assessed: an in-vivo model of supra-sacral SCI, including a group undergoing an early intervention compared with at least one control group, and reporting clinical, urodynamic, biological and/or histological data.

Results: Among the 30 studies included in the final synthesis - 9 focused on neurotransmission, 2 on the inflammatory response, 10 on neurotrophicity, 9 on electrical nerve modulation and 1 on multi-system neuroprosthetic training. Overall, 29/30 studies reported significant improvement in urodynamic parameters, regarding both the storage and the voiding phase. These findings were often associated with substantial modifications at bladder and spinal cord level, including up/downregulation of neurotransmitters and related-receptors expression, neural proliferation or axonal sprouting and a reduction of inflammatory response and apoptosis.

Conclusions: The present review supports the concept of early interventions to prevent NLUTD after supra-sacral SCI, allowing for the emergence of a potential preventive approach in the coming decades.

INTRODUCTION

Spinal cord injury (SCI) incidence is estimated between 40 and 80 new cases per million population, meaning that every year, between 250.000 and 500.000 new people become SCI worldwide[1]. Spinal cord injury is associated with many events consecutive of mechanical insults and secondary processes, including local hypoxia, ischemia, oxidative stress, reactive gliosis, excitotoxicity and scarring process[2,3]. Endogenous repair mechanisms in the central nervous system (CNS), especially at the spinal cord level, are negligible, with innate plasticity unable to re-establish the original connectivity[4]. Therefore, reorganising pathways by sprouting, unmasking, or other compensatory mechanisms may contribute to the dysfunction that develops following SCI. Since several and complex neural circuits localised at the spinal cord level contribute to the coordinated activity of the bladder and the urethral sphincters, SCI often leads to neurogenic lower urinary tract dysfunction (NLUTD). This dysfunction emerges as follow: acute supra-sacral SCI start with an initial phase of "spinal shock" resulting in detrusor and sphincter areflexia, followed by the emergence of a spinal-reflex-pathway occurring after several weeks, resulting in both storage and voiding phase dysfunction, including detrusor overactivity (DO), bladder compliance disorders (BCD) and detrusor-sphincter dyssynergia (DSD)[5]. The emergence of urinary incontinence and recurrent urinary tract infections are responsible for significant impairment of quality of life[6]. Despite many advances regarding their prevention and management over the last three decades, the associated complications are still considered the leading cause of hospitalization and the fifth cause of mortality in this specific population[5,7]. Regarding storage dysfunction, several treatments are available in a therapeutic escalation strategy in order to restore a low-pressure bladder reservoir, including antimuscarinics, β3-adrenergic agonists, intra-vesical botulinum toxin injections, as well as tibial nerve stimulation (TNS) and sacral nerve modulation (SNM), before considering augmentation cystoplasty or other urinary diversions[8,9]. Regarding voiding dysfunction, even if α-blockers are eligible, clean intermittent self-catheterisation constitute the standard of care and is often the only way to ensure a regular, complete, and low-pressure bladder emptying[8,9].

To our knowledge, current international recommendations only focus on the management of NLUTD without including any prevention stance[8,9]. In the meantime, several teams have recently reported various early interventions, focusing on neurotransmission, inflammatory

response, neurotrophicity, electrical nerve modulation or neuroprosthetic training, to prevent or attenuate NLUTD after SCI, allowing for the emergence of a potential preventive approach in the coming decades.

The purpose of the present systematic review was to synthesise the scientific literature focusing on early interventions to prevent the emergence of NLUTD after acute supra-sacral SCI.

METHODS

Information source and search strategy

The review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines[10]. The review identified articles published through April 2021 in the PubMed, Embase, ScienceDirect and Scopus databases with MeSH and non-MeSH terms regarding early intervention to prevent or attenuate NLUTD after SCI (Supplementary Table 1). In order to be exhaustive, publications identified from cross-references were added to the final synthesis if they were considered relevant, and an updated search was performed in July 2021.

Eligibility criteria

Eligibility criteria were defined following PICOS: Patient (P), Intervention (I), Comparator (C), Outcome (O), Study Design (S). An article was deemed appropriate to this literature review if it assessed: an in-vivo model of supra-sacral SCI (human or animal model) (P), including a group undergoing an early intervention - before DO, BCD or DSD has emerged - to prevent and/or attenuate storage and/or voiding phase dysfunction (I), compared with at least one control group not undergoing any early intervention (C) and reporting clinical, urodynamic, biological and/or histological data (O). No restriction on study type was established (S).

Study selection and Data extraction

Abstract and full-text screenings were performed by three reviewers independently (NV, DS, PLD). Disagreement was resolved by consensus-building with the intervention of a fourth reviewer (XB). Two reviewers performed data collection independently (NV, XB), and a standardized form was used to extract data on study methodology, characteristics of in vivo model, early intervention performed, and clinical, urodynamic, biological as well as histological outcomes. Any discrepancy concerning data collection was resolved by consensus.

Risk of bias assessment

To assess the risk of bias (RoB), included reports were reviewed by two reviewers independently (NV, XB) using the SYRCLE (SYstematic Review Center for Laboratory animal Experimentation[11]) tool to assess studies focusing on animal models and the ROBINS-I (Risk of Bias in Non-Randomised Studies - of Interventions[12]) tool to assess studies focusing on human. After independent use of SYRCLE and ROBINS-I tools, any disagreement concerning the RoB assessment was resolved by consensus-building.

Data synthesis

Data synthesis was performed through a structured presentation detailing step by step the main results associated with early interventions focusing on 1) neurotransmission, 2) inflammatory response, 3) neurotrophicity, 4) electrical nerve modulation, and 5) neuroprosthetic training.

RESULTS

Selected studies

A total of 3,792 abstracts were retrieved. After abstract screening and removal of duplicates, 48 articles were deemed eligible for full-text screening, of which 30 studies were finally included in the final synthesis (Figure 1, Supplementary Table 2).

Risk of bias in included studies

Studies focusing on animal models were often associated with an unclear RoB, and only 7 of them had an overall low RoB (Figure 2). Concerning the only human study, a low overall RoB was reported (Figure 3).

Studies characteristics

Among the 30 studies included in the final synthesis, 9 focused on neurotransmission (Table 1), 2 on inflammatory response and 10 on neurotrophicity (Table 2), 9 on electrical nerve modulation and 1 on multi-system neuroprosthetic training (Table 3).
In-vivo models included rats in 20 studies, mice in 4, dogs in 4, minipigs in 1 and humans in 1. SCI was performed between T2 and T12 by transection (SCT) in 17 studies, by Hemi-transection (SCHT) in 1, by compression (SCC) in 10 and both by transection and compression in 1. The study focusing on human SCI, exclusively included AIS A post-traumatic lesions. Regarding the clinical outcomes of interest, 28 studies reported urodynamic parameters, 5 reported metabolic cages or bladder diary related data, and 3 reported results of ex-vivo bladder strip contractility tests. Tissues were analysed in 25 studies, including bladder in 18, spinal cord in 12 and dorsal root ganglia in 2 of them.

Neurotransmission

Muscarinic pathway

Biardeau et al.*[13]* and Temeltas et al.*[14]* assessed the effect of early pre*[13]*- and post-synaptic*[14]* inhibitions of the muscarinic pathway in SCT rats. Evaluating subcutaneous fesoterodine fumarate*[13]* and bladder wall injections of botulinum toxin A*[14]*, they both reported a significant improvement in cystometric pressure parameters, associated*[13,14]*associated with a significant decrease in bladder fibrosis and hyperplasia*[14]*. Interestingly, Biardeau et al.*[13]* showed a persistent effect after a 72h wash-out period and hypothesised that the early administration of an antimuscarinic drug could act not only through an acute pharmacological effect but also by countering pathological modifications of

muscarinic pathways, mainly at the M2 and M3 receptor level. Similarly, Temeltas et al.*[14]* reported better histological and cystometric outcomes after early injections (d7) when compared with late injections (d28), while not statistically significant.

Adrenergic pathway

Lee et al.*[15]* and Kadewaka et al.*[16]* assessed the effect of early α-adrenergic inhibition in SCT rats through intraperitoneal instillation of tamsulosin*[15]* or oral naftopidil administration*[16]*. Arguing that α_{1D} -adrenergic receptor localized in the detrusor can promote acetylcholine secretion*[15]* and facilitate vasoconstriction*[15]* and facilitate vasoconstriction*[16]* at the bladder level, the authors considered that inhibition of such receptors could improve the SCI-induced bladder remodelling. Even if Lee et al.*[15] * reported no significant modification in cystometric pressure parameters - with a urodynamic study performed only one week after SCI - they reported bladder strips contractility in the presence of M3 antagonist to be significantly decreased in tamsulosin-treated SCI rats. Furthermore, in this group, pERK1/2 and Rho-kinase expressions - correlated to the activation of muscarinic receptors, particularly M2 receptors - were reported to be increased and decreased, respectively. Kadewaka et al.*[16]* reported an increase in bladder compliance and voiding efficiency associated with a decrease in urethral pressure in naftopidil-treated SCI rats. They also reported a decrease in upregulation of ischemia and fibrosis markers and collagen concentration at the bladder level early after SCI.

Nitrergic pathway

Kadewaka et al.*[16]* also assessed the effect of an early oral tadalafil administration, a phosphodiesterase type 5 inhibitor, thought to improve bladder tissue oxygenation. When comparing treated SCT rats with non-treated SCT rats, the authors reported a decrease in upregulation fibrosis markers and collagen concentration late after SCI, associated with an increase in bladder compliance.

Purinergic pathway

Munoz et al.*[17]* assessed the effect of early intrathecal instillation of P2X7R inhibitor in SCT rats. P2X7R is a purinergic receptor expressed in microglia that downplays proper tissue regeneration after SCI by enhancing inflammatory response and contributing to long-term scar formation. The authors reported a decrease in the number of NVCs associated with a decrease in microglial activation at the spinal cord level and a concomitant decrease of urothelial P2X3 receptors - an ionotropic purinergic receptor involved in the transmission of bladder afferent activity - at the bladder level.

Glutamatergic pathway

Wang et al.*[18]* assessed the effect of a replication-defective herpes simplex virus vector of kynurenine aminotransferase (HSVrd KAT II) administered through an early bladder wall injection in SCT rats. The N-methyl-D-aspartate receptor (NMDAr), found in the lumbosacral spinal cord, is an ionotropic glutamatergic receptor that has been reported to play an essential role in the micturition reflex pathway. In parallel, kynurenic acid, which synthesis is catalyzed by KAT II, acts as an endogenous non-competitive antagonist at the glycine site of the glutamate NMDAr and has been reported to directly influence the micturition reflex. With KAT II protein and mRNA levels significantly increased at the L6-S1 spinal cord level, the authors reported a significant decrease in maximum voiding pressure and maximum urethral closure pressure, associated with an increase in voiding efficiency in treated SCT rats when compared with non-treated SCT rats. They hypothesised that KAT II transport to Onuf's nucleus and then to L6-S1 parasympathetic preganglionic neurons could reduce the urethral pressure by blocking NMDAr, influencing neurotransmitter levels in the L6-S1 spinal cord and even desensitising C-fiber afferents.

GABAergic pathway

Miyazato et al.*[19]* assessed the effect of HSVrd Glutamic acid decarboxylase (GAD) administered through an early bladder wall injection in SCT rats. GAD is an enzyme that catalyses the decarboxylation of glutamate to GABA and contributes to maintaining the

significant physiological supply of GABA. After SCI, hypofunction of inhibitory GABAergic neuronal activity in the spinal cord has been suspected of contributing to the genesis of DSD and DO. The authors reported a significant association between GAD mRNA increased expression in L6-S1 dorsal root ganglia (DRG) and voiding urethral pressure decrease. Meanwhile, they did not identify associated differences regarding bladder activity and baseline urethral pressure. Together, the intrathecal administration of GABA antagonist almost completely reversed the decrease in the voiding urethral pressure. The authors hypothesised that GABA synthesis in bladder afferent pathways could inhibit Onuf's nucleus that innervates the external urethral sphincter (EUS) via the suppression of C-fiber bladder afferent activity to decrease DSD.

TRPV1 desensitization

Two studies assessed the effect of early administration of resiniferatoxin *[20]* or capsaicin*[21]* in SCT rats, using subcutaneous administration*[20]* or bladder*[21]*. Capsaicin and resiniferatoxin, one of their derivatives, are ultrapotent desensitizing agonists of transient receptor potential vanilloid-1 (TRPV1) known to be increased in urothelial cells and nerve fibres in the case of neurogenic DO. The authors reported an increased bladder capacity*[20]* and a decrease in the number of NVCs*[21]*, with some of the rats presenting with complete suppression of DO*[21]*. However, Thomas et al. reported no significant improvement in the inter-contraction interval, voiding pressure or voiding efficiency, as well as in EUS activity during both NVCs and voiding bladder contractions. After bladder instillation of resiniferatoxin, Oliveira et al.*[20]* showed decreased expressions of TRPV1, calcitonin gene-related peptide (CGRP) - two markers of peptidergic fibres - and growth-associated protein 43 (GAP43) - marker of sprouting nerve fibres - at the bladder level, with no modification of CGRP and GAP43 expressions or in the number of activating transcription factor 3 (ATF3) positive nuclei - a marker of neuronal stress - in L5-S1 DRG. The authors hypothesised that the early administration of vanilloid therapy might mitigate the development of high intravesical pressures in a long-lasting manner. It might prevent C-fiber afferents becoming hyperexcitable*[21]* by peptidergic fibres at the bladder level*[20]* without inducing damage to the DRG neurons*[20]*.

Inflammatory response

Shunmugavel et al.*[22] * assessed the effect of early oral administration of S-Nitrosoglutathione (GSNO) in SCC rats. GSNO, as an endogenous nitrosylating agent, has anti-inflammatory properties. Since it has been reported to ameliorate inflammatory sequelae observed in the bladder and renal tissues after SCI, the authors postulated that GSNO would improve the recovery of micturition dysfunction by quenching the bladder tissue inflammation associated with SCI. The authors reported that GSNO-treated SCI rats regained significant micturition control over vehicle-SCI rats. In parallel, they reported a significant decrease in bladder weight, proteinuria, urine osmolality, and immune cell infiltration and collagen deposition at the bladder level. They also reported a decrease in the mediator of inflammation expression (iNOS and ICAM-1) at the bladder and kidney level, associated with a decrease of TUNEL positive-cells at the bladder level, indicating a decrease in the apoptotic process.

David et al.*[23] * assessed the effect of early intrathecal instillation of Toll-like Receptor 9 (TR9L) inhibitor in SCC mice. TLR9 is a receptor expressed in immune system cells that triggers signaling cascades leading to a pro-inflammatory cytokine response. The authors reported a significant decrease in urinary retention associated with decreased bladder weight, bladder volume and bladder wall thickness. At the spinal cord level, the authors reported the white matter to be significantly more spared.

Neurotrophicity

Axonal growth inhibitors antagonists

Mothe et al.*[24] * and Schneider et al.*[25] * assessed the effect of early antagonization of axonal growth inhibitors using intravenous administration of elazanumab*[24]*, a human monoclonal antibody targeting Repulsive Guidance Molecule an (RGMa) and intrathecal administration of anti-Nogo A*[25]* in SCC and SCT rats, respectively. RGMa is a potent inhibitor of axonal growth that has been reported to be rapidly upregulated after injury of the central nervous system. In contrast, myelin-enriched membrane protein Nogo-A, a potent nerve fibre growth inhibitory protein, has been reported to be implicated in the low level of spontaneous

neuronal regeneration after SCI. The authors reported earlier spontaneous voiding ability*[24]* associated with a decrease in bladder wall hypertrophy*[24]*, a decrease in EUS EMG*[24]* activity, a as well as a significant decrease of maximum bladder pressure during voiding*[25]*. Mothe et al.*[24]* also reported more remarkable tissue preservation at the spinal cord level characterized by reduced lesion areas associated with increased perilesional neuronal sparing as well as serotonergic and corticospinal axonal plasticity. Schneider et al.*[25]* found higher densities of fibres originating from the pontine micturition center in the lumbosacral grey matter and a decreasing number of inhibitory interneurons in lamina X. The authors hypothesised that early and temporary neutralisation of the neurite growth inhibitory factor Nogo-A might contribute to the reconfiguration of the bladder control on spinal and supraspinal levels.

Neurotrophic factors

Two studies assessed the effect of early inhibition of neurotrophic factors in SCT mice, including oral administration of brain-derived neurotrophic factor (BDNF)*[26]* and nerve growth factor (NGF)*[27]* inhibitors. Although both reported a significant decrease in cystometric pressure parameters*[26,27]*, BDNF inhibition only reduced NVCs in a late phase following SCI, when NGF inhibition acted earlier after SCI. Furthermore, when BDNF inhibitors improved voiding dysfunction*[26]*, NGF inhibitors did not modify EUS EMG activity*[27]*. After NGF-inhibitor treatment, NGF expression was decreased at the bladder and the spinal cord level, while TRPA1 and TRPV1 expressions - predominantly found in C-fiber afferent pathways - were significantly decreased in L6/S1 DRG)*[27]*. The authors concluded that short to long-term BNDF inhibition could improve voiding dysfunction associated with DSD, while a long-term BNDF inhibition was required to reduce the later-phase development of C-fibres dependent DO. On the contrary, NGF inhibition could precociously slow down TRPV1 up-regulation, attenuate C-fibres activation and thus prevent the early emergence of DO.

On the opposite, Mitsui et al.*[28]* assessed the effect of early intrathecal administration of fibroblasts (Fb) expressing BDNF and Neurotrophin 3 (NT3) in SCC rats. According to the authors, BDNF and NT3 act as neurotrophic factors on specific neurons of the central and peripheral nervous system, helping to support the survival of existing neurons, and

encouraging growth and differentiation of new neurons and synapses. The authors reported a significant decrease in voiding pressure and in the number of NVCs. The density of small dorsal root axons increased in the superficial layers of the dorsal horn in non-treated SCI rats but not in Fb-BDNF/NT3-treated SCI rats, suggesting inhibition of sprouting of primary afferents by Fb-BDNF/NT3. Synaptophysin immunoreactivity in the lumbosacral dorsal horn was similar among treated and non-treated SCI rats, consistent with restoring synaptic density after SCI in both groups - probably through different pathways. The authors concluded that Fb-BDNF/NT3 transplant could contribute to structure and reorganise spinal circuitry after SCI.

Mure et al.*[29]* and Chung et al.*[30]* assessed the effect of early administration of neurotrophic facilitators, including administration of dehydroepiandrosterone (DHEA)*[29]* in SCC mice and inosine*[30]* in SCC/SCT rats. DHEA as a neuroactive steroid could act as a modulator of neurotrophic factor receptors and have previously been shown to promote neurological recovery after SCI. As a purine nucleoside with neurotrophic properties, inosine, has been reported to promote corticospinal tract fibers sprouting and improve motor function in pre-clinical models of SCI. Mure et al.*[29]* reported a faster recovery of autonomic bladder control in DHEA-treated SCI mice when Chung et al*[30]* reported a significant decrease in the frequency of NVC in both inosine-treated SCC/SCT rats and a significant decrease in the amplitude of NVCs in inosine-treated SCT rats. After DHEA administration*[29]*, change in function was associated with a ratio of collagen type3-type1 similar to that seen in sham-operated animals. At the same time, after inosine administration*[30]*, bladder analysis showed an increased expression of the pan-neuronal marker SYP and Aδ-fiber marker NF200 and a decreased expression of the C-fiber marker TRPV1. Mure et al.*[29]* concluded that DHEA could prevent NLUTD after SCI through its neuroprotective and neuroactive properties, including glucocorticoid and cyclooxygenase-2,12 inhibitions, or even act directly on the bladder tissue through androgen and estrogen metabolism. In addition, Chung et al.*[30]* concluded that inosine could prevent DO through modulation of sensory neurotransmission.

Neural precursor cells

Mitsui et al. assessed in three distinct studies*[31-33]* the effect of early intrathecal implantation - at the lesion site - of restricted neuronal precursor (NRP) and glial restricted precursor (GRP)

alone*[33]* or associated with 2,3-dihydroxy-6-nitro-7 sulfamoylbenzo(f)quinoxaline (NBQX)*[31]* as well as early intrathecal implantation of EG6 immortalized neural stem cells*[32]* in SCC rats. Microinjection of NBQX has been shown to significantly decrease the amount of tissue loss following SCI through inhibition of AMPA receptors contributing to the excitotoxicity mediated tissue damage that ensues within minutes following traumatic SCI. NRP/GRP alone*[33]* or associated with NBQX*[31]* were reported to increase voided volumes per micturition and improve cystometric pressure parameters, including a decrease in micturition pressure and the number of NVCs. On the contrary, EG6 cells*[32]* were reported to decrease post-void residual volume and increase voiding efficiency without impacting voided volume or DO. NRP/GRP-treated and NBQX-treated SCI rats*[31,33]* presented increased sprouting, regeneration or sparing of descending projections to the lumbosacral cord associated with a decrease in the size of the lesion.

Similarly, these rats*[31,33]* showed a decrease in the sprouting of primary afferents in the lumbosacral cord. Furthermore, in NBQX + NRP/GRP-treated SCI rats*[33]*, the density of serotonergic, noradrenergic, and corticotrophin-releasing factor-positive fibres was increased, while the density of axons in the dorsal horn appeared normal. The authors concluded that neural stem cell implantation could prevent NLUTD by providing local protection consisting of increased sparing/sprouting of descending pathways, thus preventing sprouting by dorsal root axons.

Electrical nerve modulation

Pudendal nerve modulation

Three studies assessed the effect of early 5-10 Hz pudendal nerve modulation (PNM) in SCI minipigs*[34]* and dogs*[35,36]*. They all reported a significant decrease in the number of NVCs and a significant increase in bladder capacity and compliance. Interestingly, Chen et al.*[36]* assessed this effect at different time points (early: d30, delayed: d180) and reported significant changes after early PNM-treated SCI dogs compared to baseline, while no significant change was reported after delayed PNM-treated SCI dogs. Likewise, they noted the presence of fewer collagen fibres associated with more elastin fibres in early PNM-treated SCI dogs compared with delayed PNM-treated SCI dogs. Keller et al.*[34]* directly compared 10 Hz

PNM to 10 Hz SNM and reported a significant increase in bladder capacity associated with a significant decrease in voiding pressure and DSD in SNM-treated minipigs compared to PNM-treated and non-treated SCI minipigs. Although structural results revealed SCI-typical fibrotic alterations in both SNM and PNM-treated SCI minipigs, SNM-treated SCI minipigs showed a better-balanced distribution of smooth muscle to connective tissue with a trend towards the reduced progression of bladder wall scarring.

Sacral nerve modulation

Five studies assessed the effect of early 10-60 Hz SNM in SCI animals*[34, 37-40]*. Considering SCI minipigs*[34]* and rats*[37,38]*, the authors reported a significant improvement in DO, including a decrease in the frequency and maximum pressure NVCs associated with an increase in the time between contractions the duration of contraction. In Shi et al.*[38]* study, SNM has proven to be able to decrease DO regardless of the delay between SCI and implantation. However, the authors reported SNM to be particularly efficient when implanted 2 to 4 weeks after SCI, at the end of the spinal shock phase and before the development of DO. Considering SCI dogs, Hassouna et al.*[39]* And Li et al.*[40]*, on the basis of particularly elaborate studies, reported the delay before the return of DO after a spinal shock to be significantly decreased in NMS-treated SCI dogs, when compared to SCI dogs managed with indwelling or CISC catheters, with SNM reported ensuring complete voiding up to eight months*[40]*.

Sievert et al.*[41]* assessed the effect of early SNM in supra-sacral post-traumatic AIS A SCI humans. In early SNM-treated SCI patients, the authors reported the persistence of low bladder pressure (<30cmH2O) without any NVCs or bladder compliance disorders throughout the filling phase, without any pelvic activity during a mean follow-up period of 26.2 (range 5.4 -38.9) months. The bladder diaries revealed a mean catheterised volume of 582ml (range 480-650ml). The participants did not report involuntary urine leakage, nor did they receive an antimuscarinic or botulinum toxin before their last evaluation. On the contrary, despite taking antimuscarinics, the non-treated SCI patients were reported to present with lower bladder capacity (mean 208ml; range 57-314ml) and higher bladder pressure (>30cmH2O). Furthermore, they reported mean catheterised volumes of 294ml (range, 105-390ml), with more frequent CISC and used urinary condoms because of urinary incontinence. The authors

concluded that early SNM implantation in SCI patients might dramatically change NLUTD management, as it could prevent DO and urinary incontinence and provide standard bladder capacity.

Multi-system neuroprosthetic training

Horst et al.*[42]* assessed the effect of a multi-system neuroprosthetic training (MSNT) program in bilateral T7 + T11 SCHT rats. The MSNT program included an electrochemical stimulation (epidural S2-L1 electrical stimulation associated with serotonergic and dopamine agonists administration) to locomotor treadmill-based training. This MSNT has been previously reported to trigger a massive reorganisation of descending and intra-spinal pathways in SCI rats. The authors reported a significant decrease in the number of NVCs while bladder capacity increased 3-fold in complete MSNT SCI-rats and 7-fold in partial MSNT SCI-rats. Bladder morphology was similar between complete MSNT SCI and non-SCI rats, while partial MSNT SCI rats exhibited detrusor hypertrophy characterized by increased detrusor thickness and decreased connective tissue to smooth muscle ratio. The authors also reported that the general nerve density was significantly increased in complete MSNT SCI rats while significantly decreased in partial MSNT SCI rats. The relative proportion of NF200-positive afferent nerves was significantly decreased in complete MSNT SCI rats compared to partial MSNT SCI and non-SCI rats, while NPY-positive fibres density was significantly decreased in partial MSNT SCI rats.

DISCUSSION

To our knowledge, the present systematic review is the first to synthesise the scientific literature focusing on early interventions to prevent the emergence of NLUTD after acute supra-sacral SCI. Since NLUTD remain considered the leading cause of hospitalisation and the fifth cause of mortality after SCI[7] - despite multiple advances regarding their management over the last three decades - their prevention should be considered a priority by the international scientific community in the coming decades.

The present review should not be considered as an attempt to precisely describe the complex mechanisms underlying the genesis, the consolidation and the prevention of LUTD after SCI,

but rather as a whistleblowing stance to advocate and guide for the emergence of clinical studies to prevent NLUTD in this specific population.

The high number of studies (29/30) reporting significant improvement of urodynamic parameters - clearly supports the concept of a preventive approach aiming to interfere in the anarchic reorganisation occurring below the SCI - at least in some animal models. Early interventions were mostly reported to inhibit C-fibres hyperexcitability and promote neuroplasticity, including the promotion of sprouting, regeneration or sparing of descending projections to the lumbosacral cord as well as the inhibition of sprouting of primary afferents in the lumbosacral cord. However, methodological heterogeneity between included studies - type of approaches tested, designs of the studies reported, types of in-vivo model studied, outcomes considered, frequent unclear to high RoB - prevent us from drawing any definitive conclusion on the best strategy to promote. Although all the proposed approaches deserve to be explored in humans, some of them will be difficult to consider in the early phase of SCI, given the time-consuming, complex and invasive care that will be associated with. For these reasons, we feel that some orally administered drugs (antimuscarinic, α-blocker and phosphodiesterase type 5 inhibitor) and electrical nerve modulation appear as the most mature candidates for a medium-term application in humans. Electrical nerve modulation with 9 studies reported here, including 1 in humans, is the therapeutic approach for which we have the longest experience and visibility, with SNM and TNS - two mini-invasive therapies - already considered as second-line therapies to treat NLUTD[8,9]. This position is supported by recent findings suggesting that manipulation of neuronal activity can drive plasticity-related growth mechanisms and increase collateral sprouting, thereby enhancing the functional effect of axonal remodeling[43]. Furthermore, even if electrical stimulation has long been known to enhance regeneration of peripheral axons[44], it has been reported recently that electrical modulation could also enhance CNS plasticity in rodent models and modulate and strengthen spared circuitry in individuals with SCI[45-49]. However, given the limited data available in humans, it is impossible to propose electrical nerve modulation therapies as a preventive approach for SCI-related NLUTD in our clinical practice. Randomised clinical trials, such as the TASCI research protocol (transcutaneous tibial nerve stimulation in patients with acute spinal cord injury to prevent neurogenic detrusor overactivity) proposed by Birkhäuser et al.[50] are mandatory to confirm the interest of such a preventive strategy in SCI-humans, both in the short- and long-term period.

CONCLUSION

The present systematic review supports the concept of early interventions to prevent NLUTD after SCI, allowing for the emergence of a potential preventive approach. Electrical nerve modulation should be considered today as the most mature strategy for a medium-term application in humans.

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Figure 1: PRISMA flow diagram

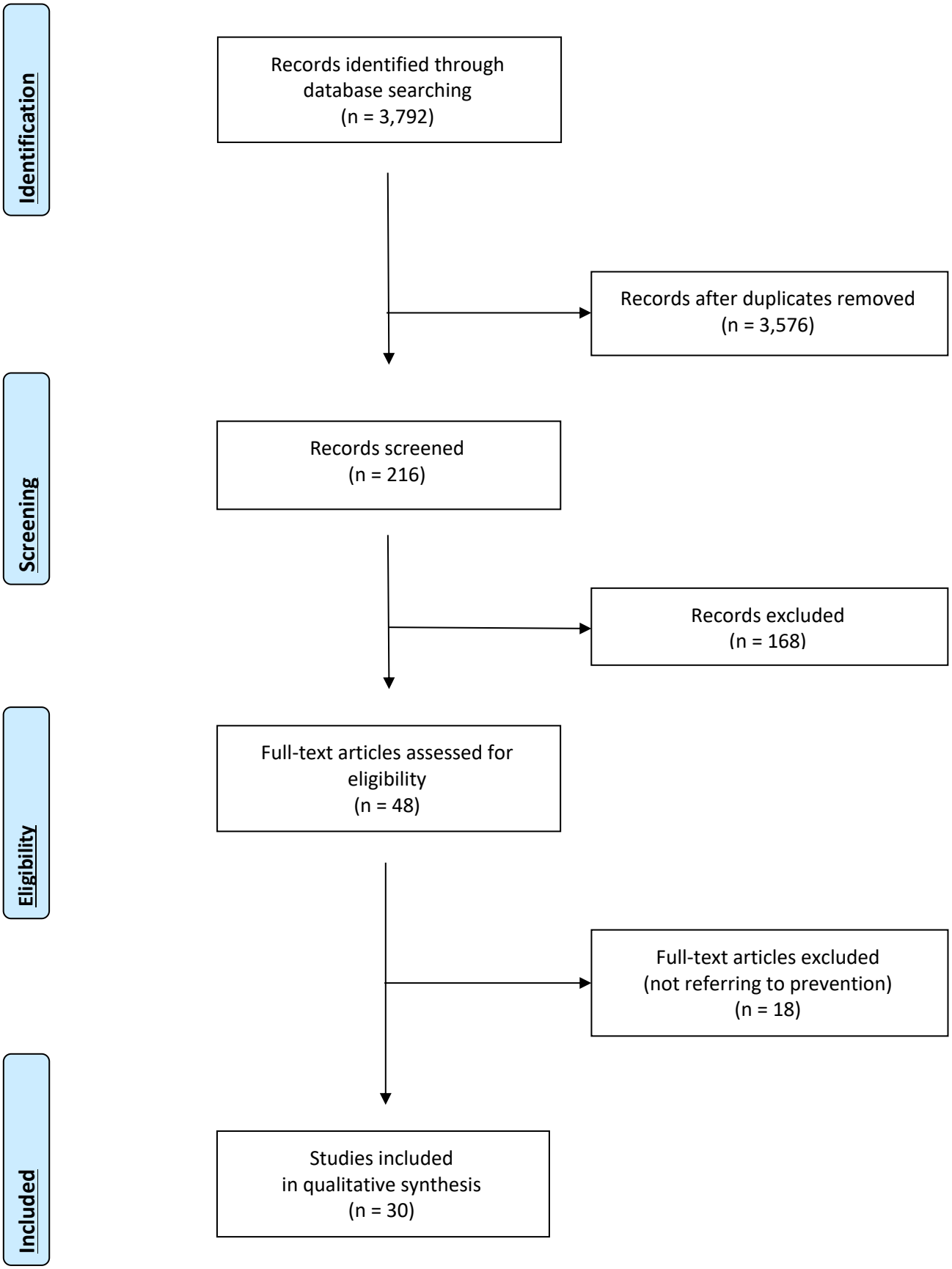
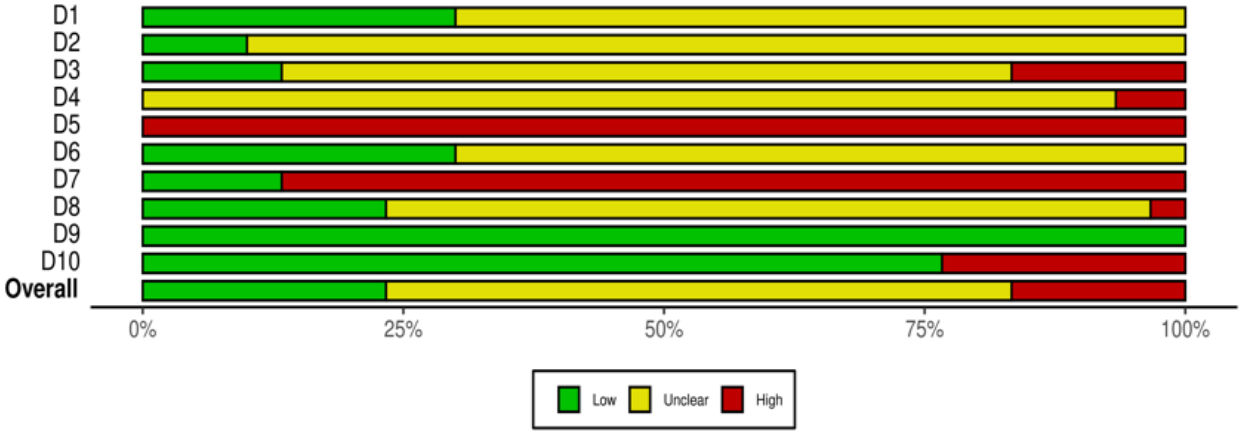


Figure 2: Risk of bias assessment - SYRCLE tool - Summary



Domains:
D1: Bias due to sequence generation.
D2: Bias due to baseline characteristics.
D3: Bias due to allocation concealment.
D4: Bias due to random housing.
D5: Bias due to blinding (performance).
D6: Bias due to random outcome assessment.
D7: Bias due to blinding (detection).
D8: Bias due to incomplete outcome data.
D9: Bias due to selective outcome data.
D10: Bias due to other source of bias.

Figure 3: Risk of bias assessment - ROBINS-I tool - Traffic-light plot

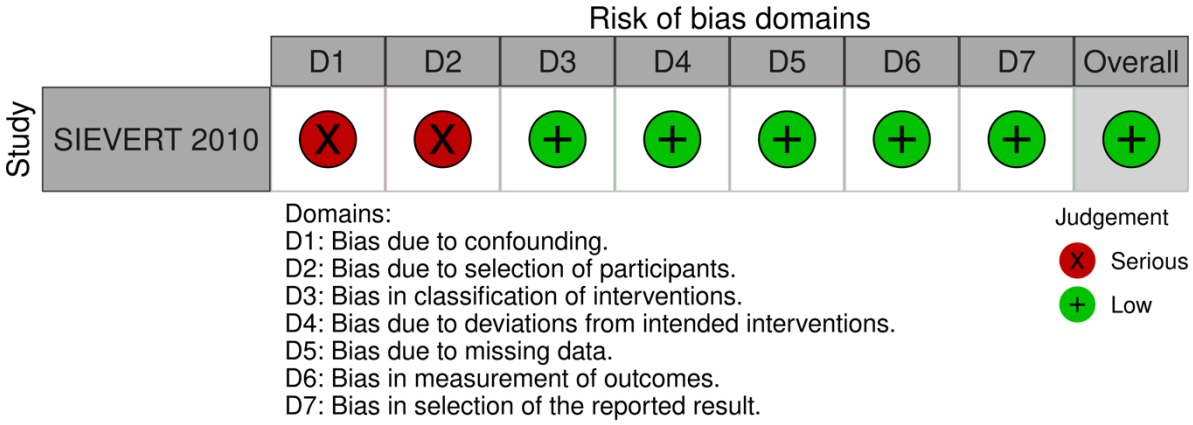


Table 1: Characteristics of studies focusing on neurotransmission

First author Year	*In-vivo* model	Level of SCI Type of SCI	Intervention Mode of administration	Groups (delay after SCI)	Clinical and Urodynamic outcomes (delay after SCI)	Biology and Tissue analysis outcomes (delay after SCI)
Muscarinic pathway						
BIARDEAU 2017 Ref 13	Rats	**T10** Transection	**Fesoterodine** Sub-cutaneous	3 non-SCI 6 SCI 6 SCI + Fesoterodine 0.12 mg/kg (d0) 6 SCI + Fesoterodine 0.18 mg/kg (d0) 6 SCI + Fesoterodine 0.12 mg/kg (d0) + 72h WO 6 SCI + Fesoterodine 0.18 mg/kg (d0) + 72h WO	**Metabolic cages (d21, 28, 35)** Voided volume ; Voiding frequency **Urodynamic - awake - supra-pubic (d42)** Baseline pressure ; Intermicturition pressure ; Treshold pressure ; Maximum pressure ; Bladder capacity ; Voided volume ; Post-void residual volume	
TEMELTAS 2005 Ref 14	Rats	**T9-T10** Transection	**Onabotulinum-A toxin** Bladder wall injection	6 non-SCI 6 SCI 5 SCI + Onabotulinum-A toxin 2-3U (d7) 5 SCI + Onabotulinum-A toxin 2-3U (d28) 5 SCI + vehicle (d28)	**Urodynamic - anesthetized - urethral (d0, d42)** Baseline pressure ; Opening pressure ; Frequency and Amplitude of NVC Bladder capacity	**Bladder tissue (d42)** Fibrosis ; Epithelial desquamation ; Hyperplasia
Adrenergic pathway						
KADEKAWA 2017 Ref 16	Rats	**T9-T10** Transection	**Naftodipil / Tadalafil** Oral	6/8 non-SCI 6/8 SCI + vehicle (d7) 6/8 SCI + Naftopidil 20 mg/kg/day (d7) 6/8 SCI + Tadalafil 2 mg/kg/day (d7)	**Urodynamic - anesthetized** **urethral / supra-pubic (d14, 28, 56, 84)** Bladder capacity ; Intercontraction interval ; Maximum voiding pressure ; Baseline pressure ; Number of NVC ; Voided volume ; Post-void residual volume ; Urethral pressure	**Bladder (d7,14, 28, 56, 84)** Weight Collagen (type 1,3) ; Elastin TGF-β1 ; HIF-1α ; VEGF
LEE 2014 Ref 15	Rats	**T10** Transection	**Tamsulosin** Intra-peritoneal instillation	12 non-SCI 12 SCI 21 SCI + Tamsulosine 0.1 mg/kg (d0)	**Urodynamic - awake - supra-pubic (d7)** Baseline pressure ; Maximunl pressure ; Voided volume ; Voiding frequency ***Ex-vivo* bladder strips contractility (d7)** Acetylcholine ± M2 antagonist and M3 antagonist	**Bladder (d7)** ERK1/2; pERK1/2 ; rho-kinase
Nitrinergic pathway						
KADEKAWA 2017 Ref 16	Rats	**T9-T10** Transection	**Naftodipil / Tadalafil** Oral	6/8 non-SCI 6/8 SCI + vehicle (d7) 6/8 SCI + Naftopidil 20 mg/kg/day (d7) 6/8 SCI + Tadalafil 2 mg/kg/day (d7)	**Urodynamic - anesthetized** **urethral / supra-pubic (d14, 28, 56, 84)** Bladder capacity ; Intercontraction interval ; Maximum voiding pressure ; Baseline pressure ; Number of NVC ; Voided volume ; Post-void residual volume ; Urethral pressure	**Bladder (d7,14, 28, 56, 84)** Weight Collagen (type 1,3) ; Elastin TGF-β1 ; HIF-1α ; VEGF
Purinergic pathway						
MUNOZ 2017 Ref 17	Rats	**T8-T9** Transection	**P2X7R inhibitor** Intrathecal instillation	6 non-SCI 6 SCI 6 SCI + vehicule (d0) 6 SCI + P2X7R antagonist (d0)	**Urodynamic - anesthetized - supra-pubic (d28)** Maximum voiding pressure ; Duration of intra-luminal pressure HFO Frequency of NVC ; Voided volume	**Bladder (d28)** P2X3R **Spinal cord (d28)** P2X7R
Glutamatergic pathway						
WANG 2017 Ref 18	Rats	**T10** Transection	**HSVrd KAT II** Urethral wall injection	12 SCI + vehicle (d7) 12 SCI + HSVrd (d7) 12 SCI + HSVrd KAT II (d7)	**Urodynamic - anesthetized - supra-pubic (d21)** Maximum urethral closure pressure ; Number and amplitude of NVC ; Maximum voiding pressure Bladder capacity ; Voided volume ; Voiding efficiency ; Time to first NVC ; voiding time	**Spinal cord (d28)** KAT II Actin Ratio of KAT II /actin KAT II mRNA
GABAergic pathway						
MIYAZATO 2010 Ref 19	Rats	**T9-T10** Transection	**HSV GAD** Bladder wall injection	*Experiment 1* 10 SCI (d7) 8 SCI + HSV LacZ (d7) (control) 10 SCI + HSV GAD (d7) *Experiment 2* 5 SCI + HSV GAD (d7) Intrathecal GABA-r antagonist during UDS *Experiment 3* 4 SCI + HSV LacZ (d7) (control) 4 SCI + HSV GAD (d7)	*Experiment 1* **Urodynamic - awake- urethral / supra-pubic (d28)** Baseline urethral pressure ; Urethral pressure at the peak of bladder contractions ; Interval and Amplitude of bladder contractions ; Baseline intra-vesical pressure *Experiment 2* **Urodynamic - awake- urethral / supra-pubic (d28)** ***Before/After Intrathecal GABA receptor antagonist*** Baseline urethral pressure ; Urethral pressure at the peak of bladder contractions ; Interval and Amplitude of bladder contractions ; Baseline intra-vesical pressure	*Experiment 3* **Dorsal root ganglia (d28)** GAD mRNA
TRPV1 desensitization						
OLIVEIRA 2019 Ref 20	Rats	**T8-T9** Transection	**Resiniferatoxin** Bladder instillation	4 sham SCI 4 SCI control 4 SCI + vehicle (d0) 8 SCI + vehicle (d3 and d9) 4 SCI + Resiniferatoxin 50 nM (d0) 8 SCI + Resiniferatoxin 50nM (d3 and d9) 4 SCI sham + vehicle (d3 and d9) 4 SCI sham + Resiniferatoxin 50nM (d3 and d9)	**Urodynamic – anesthetized – supra-pubic (d28)** Frequency and Amplitude of NVC ; Baseline and Peak pressure of NVC	**Bladder (d28)** TRPV1 ; CGRP ; GAP43 **Spinal cord + dorsal root ganglia (d28)** CGRP ; GAP43 **Dorsal root ganglia culture (d28)** Quantification of neurite branching ; Quantification of total neurite length ATF3 ;
THOMAS 2007 Ref 21	Rats	**T9-T10** Transection	**Capsaicin** Sub-cutaneous	6 SCI 5 SCI + capsaicin (d-4 and d5) 6 SCI + capsaicin (d28)	**Urodynamic - awake- supra-pubic (28)** Intercontraction intervals ; Voiding pressure ; Number of NVC ; Voiding efficiency ; **External urethral sphincter EMG (d28)** (In 2 SCI rats)	

Ref : refers to on-line supplement (Supplementary Table 2)

SCI: spinal cord injury ; **NVC:** non-voiding contraction ; **ERK1/2**: extracellular signal-regulated kinases 1/2 ; **pERK1/2**: phosphorylated extracellular signal-regulated kinases 1/2 ; **TGF-β1:** transforming growth factor beta 1; **HIF-1α:** hypoxia inducible factor 1 alpha ; **VEGF:** vascular endothelial growth factor ; **GABA:** gamma-aminobutyric acid ; **EMG**: electromyogram ; **HSVrd:** replication-defective herpes simplex virus vector ; **GAD**: glutamic acid decarboxylase ; **UDS:** urodynamic study ; **KAT II:** kynurenine aminotransferase ; **P2X3:** P2X purinergic receptor 3 ; **P2X7:** P2X purinergic receptor 7 ; **TRPV1:** Transient receptor potential vanilloid 1 ; **GAP43:** growth-associated protein 43 ; **CGRP:** calcitonin gene-related peptide ; **ATF3:** activating transcription factor 3

Table 2: Characteristics of studies focusing on inflammatory response and neurotrophicity

First author Year	*In-vivo* model	Level of SCI Type of SCI	Intervention Mode of administration	Groups (delay after SCI)	Clinical and Urodynamic outcomes (delay after SCI)	Biology and Tissue analysis outcomes (delay after SCI)
Inflammatory response						
SHUNMUGAVEL 2015 Ref 22	Rats	**T9-T10** Compression	**GSNO** Oral	12 SCI 10 SCI + vehicle (h1) 10 SCI + GSNO (h1)	**Urodynamic - anesthetized - supra-pubic (d2, 14)** Intercontraction intervals ; Voiding pressure Number of voidings ; Voided volume	**Urinanalysis (d2, 14)** Weight ; Protein ; Osmolality **Bladder (d2, 14)** Weight ; Detrusor morphology ICAM-1; iNOS ; TUNEL-positive cells **Kidney (d2, 14)** ICAM-1; iNOS ; TUNEL-positive cells
DAVID 2014 Ref 23	Mice	**T8** Compression	**TLR9 inhibitor** Intrathecal instillation	X non-SCI X SCI + vehicle (d1) X SCI + TRL9 inhibitor (CpG ODN 2088), (d1)	**Evaluation of bladder function** Weight of urine voided (every 12h) Water intake (every 48h)	**Urinanalysis (d7, 14, 28)** Ketones ; Bilirubin ; Protein, Nitrites ; Leukocytes ; pH **Bladder (d28)** Bladder weight and volume ; Bladder wall thickness **Kidney (d28)** Glomerulopathy ; Interstitial inflammation ; Fibrosis **Spinal cord (d28)** Lesion volume ; Spared white and grey matter
Neurotrophicity						
Axonal growth inhibitors antagonists						
MOTHE 2020 Ref 24	Rats	**T8-T9** Compression	**Elazanumab** Intra-veinous	8 SCI 10 SCI + Elazanumab 25mg/kg (h0) 9 SCI + Elazanumab 25mg/kg (h3) 8 SCI + Elazanumab 25mg/kg (h24) 9 SCI + hIgG (h0) (control)	**Voiding ability** Ability to void on its own And without requiring manual pressure And during 3 consecutive days	**Bladder (d84)** Thickness of the detrusor muscle layer **Spinal cord (d84)** Percentage of lesion area Anterograde axonal tracing with BDA Immunostaining NeuN ; 5-HT ; BDA
SCHNEIDER 2019 Ref 25	Rats	**T8** Transection	**Anti-Nogo A antibodies** Intrathecal instillation	17 non-SCI 17 incomplete SCI + vehicle (d0) 16 incomplete SCI + Anti-Nogo A (d0) 10 complete SCI + vehicle (d0) 11 complete SCI + Anti-Nogo A (d0)	**Urodynamic – awake – supra-pubic + External urethral sphincter EMG (d7,14,21,28)** Maximum detrusor pressure ; Bladder compliance Maximum flow rate ; Voiding time ; Voided volume External urethral sphincter EMG analysis	**Spinal cord** Percentage of spared white matter ; CRF ; Glycinergic interneurons ; GABAergic interneurons ; Glutamatergic interneurons
Neurotrophic factors						
WADA 2020 Ref 26	Mice	**T8-T9** Transection	**BDNF inhibitor** Sub-cutaneous	29 SCI 16 SCI + anti-BDNF antibodies (d7) 16 SCI + anti-BDNF antibodies (d27)	**Urodynamic - awake- supra-pubic (d10,20,30)** Bladder capacity ; Number of NVC ; Treschold pressure ; Maximum voiding pressure ; Voided volume ; Post-void residual volume ; Voiding efficiency ; Notch-like periods *(synergistic activity between the bladder and the external urethral sphincter)*	**Bladder (d2, 14)** BDNF
WADA 2018 Ref 27	Mice	**T8-T9** Transection	**NGF inhibitor** Sub-cutaneous	10 SCI 10 SCI + anti-NGF for 7 days (d21) 8 SCI + anti-NGF for 14 days (d21)	**Urodynamic - awake- supra-pubic + External urethral sphincter EMG (d28)** Bladder capacity ; Number of NVC ; Treschold pressure ; Maximum voiding pressure ; Voided volume ; Post-void residual volume ; Voiding contraction time EMG activity duration	**Bladder (d28)** NGF TRPA1 ; TRPV1 ; P2X3 **Spinal cord (d28)** NGF
MITSUI 2004 Ref 28	Rats	**T8-T9** Compression	**Fibroblasts expressing BDNF/NT3** Intrathecal instillation	6 non-SCI 11 SCI + vehicle (d9) 12 SCI + Fb-BDNF/NT3 (d9)	**Urodynamic - awake - supra-pubic (d56)** Maximum voiding pressure ; Frequency of NVC ; Bladder capacity ; Voided volume ; Post-void residual volume ;	**Spinal cord (d56)** Volume of normal spinal cord 5-HT ; CRF ; GAP43 ; CGRP VR-1 ; DβH ; synaptophysin
CHUNG 2015 Ref 30	Rats	**T8** Transection Compression	**Inosine** Intra-peritoneal instillation	5 SCI (transection) + vehicle(d0) 4 SCI (transection) + Inosine (d0) 6 SCI (compression) + vehicle (d0) 5 SCI (compression) + Inosine (d0) 6 SCI (compression) + vehicle (d56) 3 SCI (compression) + inosine (d56)	**Urodynamic - awake - supra-pubic (d42)** *(d98 if intervention = d56)* Frequency and Amplitude of NVC ; Compliance ; Peak pressure ; Voided volume ***Ex-vivo* bladder strips contractility (d42)** Phenylephrine ; Carbachol ; Electrical field stimulation ; α,β- methylene-ATP	**Bladder (d42)** SYP ; NF200 ; TRPV1 ; VAChT
MURE 2004 Ref 29	Mice	**T8** Compression	**DHEA** Sub-cutaneous + Oral + Lesion site	12 SCI + vehicle (d0) 12 SCI + DHEA (d0) 10 sham SCI + vehicle (d0) 6 sham SCI + DHEA (d0) 10 SCI + vehicle (d0) 10 SCI + DHEA (d0)	**Voiding ability** Ability to void in response to external stimuli ; Or Ability to void spontaneously	**Bladder (d42)** Thickness of the detrusor muscle layer Number of neuclei in the detrusor Collagen type I and III **Spinal cord (d42)** Area of spared white matter
Neural precursor cells						
MITSUI 2011 Ref 31	Rats	**T8-T9** Compression	**NRP/GRP + NBQX** Intrathecal instillation	10 SCI 10 SCI + NRP/GRP (d9) 10 SCI + NBQX (d0) + NRP/GRP (d9)	**Metabolic cages (d-1, 7, 14, 21, 28, 35, 42, 49, 56)** Voided volume per micturition **Urodynamic - awake - supra-pubic (d56)** Maximum voiding pressure ; Frequency of NVC ; Bladder capacity ; Voided volume ; Post-void residual volume ;	**Spinal cord (d56)** Volume of normal spinal cord Projection patterns at L6-S1
MITSUI 2005 Ref 33	Rats	**T8-T9** Compression	**NRP/GRP** Intrathecal instillation	6 non-SCI 10 SCI 10 SCI + NRP GRP (d9)	**Metabolic cages (d-1, 7, 14, 21, 28, 35, 42, 49, 56)** Voided volume per micturition **Urodynamic - awake - supra-pubic (d56)** ***Before/After Intrathecal Tamsulosin*** Maximum voiding pressure ; Frequency of NVC ; Bladder capacity ; Voided volume ; Post-void residual volume	**Spinal cord (d56)** Volume of normal spinal cord Projection patterns at L6-S1 MAP2 ; RIP ; NeuN ; GFAP ; nestin ; SYP
MITSUI 2003 Ref 32	Rats	**T8-T9** Compression	**EG6 *immortalized neural stem cells*** Intrathecal instillation	6 SCI + vehicle(d9) 6 SCI + EG6 cells BrdU labeled(d9)	**Metabolic cages (d14, 28)** Voided volume per micturition **Urodynamic - awake - supra-pubic (d28)** Intra-vesical pressure ; Bladder capacity ; Voided volume ; Post-void residual volume ;	**Spinal cord (d56)** BrdU immunoreactive-cells

Ref : refers to on-line supplement (Supplementary Table 2)

SCI: spinal cord injury ; **GSNO:** S-Nitrosoglutathione ; **ICAM-1:** intercellular adhesion molecule 1 ; **iNOS:** inducible nitric oxide synthase **; TUNEL:** terminal deoxynucleotidyl transferase-mediated biotinylated UTP nick end labeling **; TLR9:** toll-like receptor 9 ; **hIgG:** human immunoglobulin G **; TLR9:** toll-like receptor 9 ; **BDA:** biotinylated dextran amine ; **5-HT:** 5-hydroxytryptamine ; **CRF:** corticotropin releasing factor ; **BDNF:** brain-derived neurotrophic factor ; **EMG:** electromyogram; **NGF:** nerve growth factor ; **TRPA1:** transient receptor potential cation channel A1; **TRPV1:** transient receptor potential vanilloid 1 ; **P2X3:** P2X purinergic receptor 3 ; **NT3:** Neurotrophin 3 ; **GAP43:** growth-associated protein 43 ; **CGRP:** calcitonin gene-related peptide ; **VR1:** vanilloid receptor type 1 ; **DβH:** dopamine-beta-hydroxylase ; **NVC:** non-voiding contraction ; **SYP:** synaptophysin ; **NF200**: neurofilament 200 ; **TRPV1:** transient receptor potential vanilloid 1 ; **VAChT:** anti-vesicular acetylcholine transferase ; **DHEA:** dehydroepiandrosterone ; **NRP:** neuronal restricted precursor ; **GRP:** glial restricted precursor ; **NBQX:** 2,3-dihydroxy-6-nitro-7 sulfamoylbenzo(f)quinoxaline ; **MAP2:** microtubule-associated protein-2 ; **RIP:** receptor interacting-protein ; **GFAP:** glial fibrillary acidic protein ; **BrdU:** 5-bromo-2-deoxyuridine

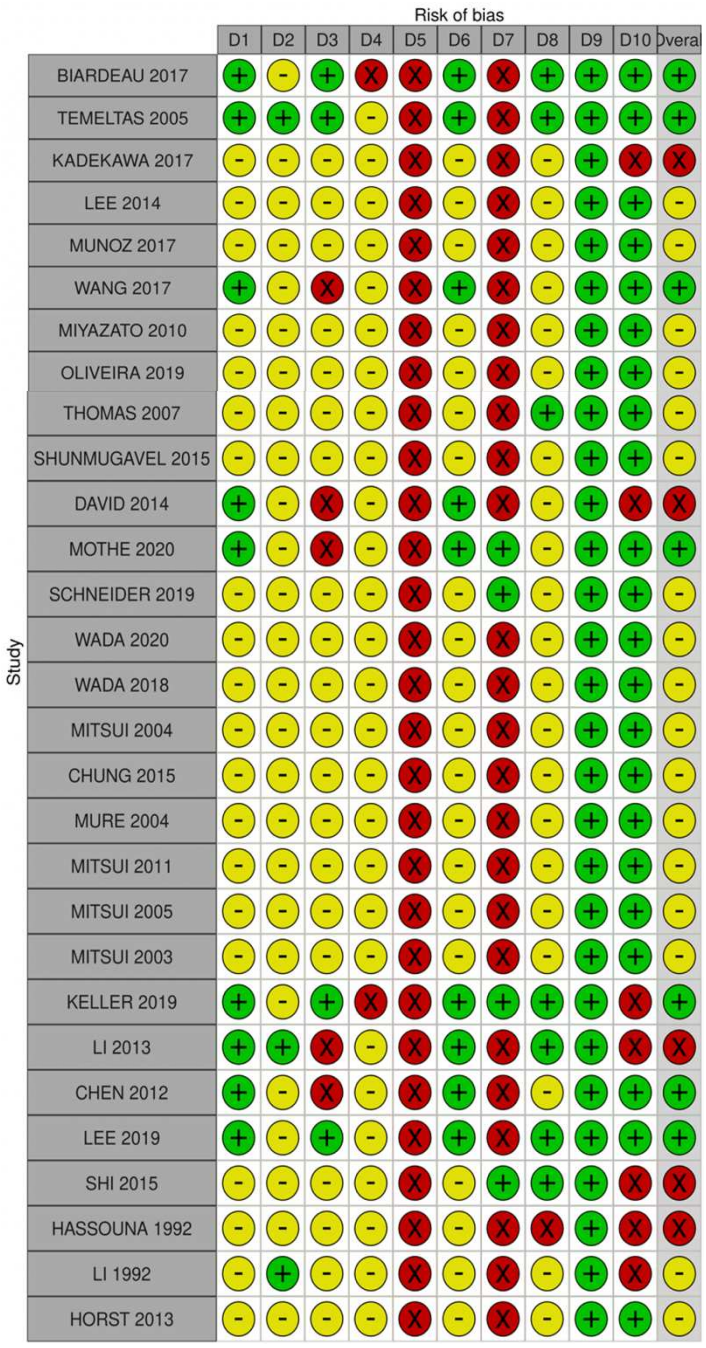
Table 3: Characteristics of studies focusing on electrical nerve modulation and multi-system neuroprosthetic training

First author Year	*In-vivo* model	Level of SCI Type of SCI	Intervention Mode of administration	Groups (delay after SCI)	Clinical and Urodynamic outcomes (delay after SCI)	Biology and Tissue analysis outcomes (delay after SCI)
Electrical nerve modulation						
Pudendal nerve modulation						
KELLER 2019 Ref 34	Minipigs	**T11-T12** Compression	**Nerve modulation** Pudendal, unilateral Sacral S3, unilateral	3 SCI 4 SCI + PNM 10 Hz (d7) 4 SCI + SNM 10 Hz (d7)	**Urodynamic - awake - urethral + peri-anal skeletal muscle EMG (d7, then every week until d112)** Detrusor overactivity ; Maximum voiding pressure Compliance ; Bladder capacity Intravesical pressure Leak point pressure ; Electromyographic activity	**Bladder (d112)** Wall thickness Wall composition and structure
LI 2013 Ref 35	Dogs	**T9-T10** Transection	**Nerve modulation** Pudendal	3 SCI 3 SCI + PNM 5 Hz (d1)	**Urodynamic - anesthetized - urethral (d0, 30, 90)** Number of NVC ; Bladder Compliance ; Bladder capacity	**Bladder (d90)** Collagen fibers ; Elastin fibers
CHEN 2012 Ref 36	Dogs	**T9-T10** Transection	**Nerve modulation** Pudendal	4 SCI + PNM 5 Hz *during UDS* (d30) 4 SCI + PNM 5 Hz *during UDS* (d180)	**Urodynamic - anesthetized - urethral (d30, 180)** Number of NVC ; Bladder Compliance ; Bladder capacity	**Bladder (d90)** Collagen fibers ; Elastin fibers
Sacral nerve modulation						
KELLER 2019 Ref 34	Minipigs	**T11-T12** Compression	**Nerve modulation** Pudendal, unilateral Sacral S3, unilateral	3 SCI 4 SCI + PNM 10 Hz (d7) 4 SCI + SNM 10 Hz (d7)	**Urodynamic - awake - urethral + peri-anal skeletal muscle EMG (d7, then every week until d112)** Detrusor overactivity ; Maximum voiding pressure Compliance ; Bladder capacity Intravesical pressure Leak point pressure ; Electromyographic activity	**Bladder (d112)** Wall thickness Wall composition and structure
LEE 2019 Ref 37	Rats	**T9-T10** Compression	**Nerve modulation** Sacral S2-S3, bilateral	7 non-SCI 7 SCI + sham SNM (d7) 7 SCI + SNM 20 Hz (d7)	**Urodynamic - anesthetized - urethral (d35)** Interval between bladder contractions ; Maximum voiding pressure ; Number of NVC ; Maximum NVC pressure	
SHI 2015 Ref 38	Rats	**T9-T10** Transection	**Nerve modulation** Sacral S1, unilateral	1 SCI + SNM *during 6 hours* (d7) 1 SCI + SNM *during 6 hours* (d12) 1 SCI + SNM *during 6 hours* (d15) 1 SCI + SNM *during 6 hours* (d18) 1 SCI + SNM *during 6 hours* (d20) 1 SCI + SNM *during 6 hours* (d27) 1 SCI + SNM *during 6 hours* (d36) 1 SCI + SNM *during 6 hours* (d42)	**Urodynamic - anesthetized - urethral (before and after 6-hours SNM)** Interval between bladder contractions ; Bladder contractions duration ; Peak bladder pressure ; Number of NVC	
HASSOUNA 1992 Ref 39	Dogs	**T10** Transection	**Nerve modulation** Sacral, bilateral	6 chronic SCI + intermittent catheterization 6 chronic SCI + undwelling catheterization 6 chronic SCI + SNM 20-60 Hz (long-term experiment)	**Cystography** Vesico-ureteral reflux **Intra-venous pyelography** Degree of hydronephrosis **Urodynamic - awake- urethral** (every week during 1m, then every month during 5m) Return of detrusor activity Maximum intra-vesical pressure Spontaneous voiding Bladder capacity	**Blood parameters** Creatinine ; Urea
LI 1992 Ref 40	Dogs	**T10** Transection	**Nerve modulation** Sacral	5 SCI + intermittent catheterization (IC) (d0) 5 SCI + IC (d0) followed by SNM (w4-6) 5 SCI + SNM (d0) 5 SCI + SNM (d0) followed by IC (w4-6)	**Cystography** Vesico-ureteral reflux Bladder neck ; Bladder contour **Intra-venous pyelography** Degree of hydronephrosis **Urodynamic - anesthetized – urethral (m6-8)** (every week during 1m, then every month during 5-7m) Amplitude and Duration of bladder contractions Bladder capacity Post-void residual volume ***Ex-vivo* bladder strips contractility (m6-8)** Urecholine	**Bladder (m6-8)** Acetylcholine content
SIEVERT 2010 Ref 41	Humans	**T2-T11** Traumatic ASIA A	**Nerve modulation** Sacral S3, bilateral	6 SCI 10 SCI + SNM, bilateral (m2.9 ; 0.8-4.5)	**Three-day Bladder diary (m3, 6)** Bladder capacity Urinary incontinence Urinary tract infections **Quality of life – Auto-questionnaires (m3, 6)** **Video-Urodynamic - awake- urethral + peri-anal skeletal muscle EMG (m3, m6, then every 6 monts)** Detrusor overactivity Compliance Bladder capacity Electromyographic activity	
Multi-system neuroprosthetic training						
HORST 2013 Ref 42	Rats	**T7+T11** Bilateral hemi-section	**Multi-system neuroprosthetic training (MSNT program)**	4 non-SCI 4 SCI + Partial MSNT program (d7) *(Epidural stimulation alone)* 4 SCI + Complete MSNT program (d7) *(Epidural stim. + Locomotor training + 5-HT + dopamine)*	**Urodynamic - anesthized- urethral (d56)** Number of NVC ; Bladder capacity ; Leak point pressure ;	**Blood analysis (d56)** Creatinine ; Cystatin C **Bladder (d56)** Detrusor thickness PGP-9.5 ; NPY ; NF200 ; TH ; VAChT

Ref : refers to on-line supplement (Supplementary Table 2)

SCI: spinal cord injury ; **EMG**: electromyogram ; **PNM:** pudendal nerve modulation ; **SNM:** sacral nerve modulation ; **NVC:** non-voiding contraction ; **UDS:** urodynamic study ; **PGP-9.5:** protein gene product 9.5; **NPY:** Neuropeptide Y ; **NF200:** neurofilament 200 ; **TH**: tyrosine hydroxylase ; **VAChT:** anti-vesicular acetylcholine transferase

Supplementary Figure 1: Risk of bias assessment - SYRCLE tool - traffic-light plot



Domains:
D1: Bias due to sequence generation.
D2: Bias due to baseline characteristics.
D3: Bias due to allocation concealment.
D4: Bias due to random housing.
D5: Bias due to blinding (performance).
D6: Bias due to random outcome assessment.
D7: Bias due to blinding (detection).
D8: Bias due to incomplete outcome data.
D9: Bias due to selective outcome data.
D10: Bias due to other source of bias.

Supplementary Table 1: Research strategy used in PubMed

Text availability	Limited to full-text article
Article type	No filter
Publication date	No filter
Species	No filter
Language	No filter
Sex	No filter
MeSH terms	[("prophylaxis") OR ("preventive therapy") OR ("preventive measures") OR ("early medical intervention")] AND [("spinal cord injuries")] AND [("urination disorder") OR ("urinary incontinence") OR ("urinary retention")]
non-MeSH terms	[("early") OR ("prevention") OR ("preventive")] AND [("spinal cord")] AND [("overactive bladder") OR ("detrusor overactivity") OR ("voiding disorder") OR ("voiding dysfunction") OR ("urgency") OR ("urinary incontinence") OR ("nocturia") OR ("lower urinary tract disorder") OR ("lower urinary tract dysfunction") OR ("urinary retention") OR ("dyssynergia") OR ("storage") OR ("voiding")]

Supplementary Table 2: Primary studies included in qualitative synthesis

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RESPONSE TO TIBIAL AND SACRAL NERVE MODULATION IN OVERACTIVE BLADDER: IS THERE ANY CORRELATION?

Secondly, we questioned the relation, in terms of efficacy, between transcutaneous tibial neurostimulation and sacral neuromodulation.

Indeed, these two electrical stimulation/modulation therapies can potentially follow each other in our therapeutic algorithms. Clarifying this point could enable us to better support our patients in the shared decision making process.

These results may also help us to understand the mechanisms of action of these two therapies. Indeed, for some, these two approaches could be considered as one and the same therapy, with the difference that one directly targets the sacral root, while the other acts at a distance. However, to date, there is no data to confirm or refute this hypothesis.

The retrospective work presented below was published in the journal *Neurourology and Urodynamics* in 2024 (156).

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ABSTRACT

Objectives: To assess the correlation between the response to transcutaneous tibial nerve stimulation (TTNS) and subsequent response to sacral nerve modulation (SNM) to treat overactive bladder (OAB).

Methods: All patients who consecutively received TTNS followed by a two-stage SNM between January 2016 and June 2022 to treat OAB in two university hospital centers were included. The response to each therapy was evaluated with success defined by a 50% or greater improvement in one or more bothersome urinary symptoms from baseline. The primary endpoint was the statistical relationship between the response to TTNS and the response to SNM, assessed by logistic regression. Secondary endpoints were the statistical relationship between the response to TTNS and the response to SNM when controlling for gender, age (< 57 yo vs > 57 yo), presence of an underlying neurological disease, and presence of detrusor overactivity, adding the factor and interaction to the previous regression model.

Results: Among the 92 patients enrolled in the study, 68 of them were women (73.9%), and the median age was 57.0 [41.0-69.0] years. The success was reported in 22 patients (23.9%) under TTNS and 66 patients (71.7%) during the SNM test-phase. There was no statistical correlation between response to TTNS and response to SNM in the overall population (CI95% [0.48 - 4.47] - p=0.51). Similarly, there was no statistical correlation when controlling for age <57yo or ≥57yo, with p=1.0 and p=0.69, respectively. No statistical study could be conducted for the other subpopulations due to small sample sizes.

Conclusion: The response to TTNS does not predict the response to SNM in the treatment of OAB. TTNS and SNM should be considered as separate therapies, and the decision-making process for OAB treatment should take this into account.

INTRODUCTION

The International Continence Society (ICS) defines overactive bladder (OAB) syndrome as the occurrence of urgency, usually accompanied by urinary frequency and/or nocturia, with or without urinary incontinence, in the absence of urinary tract infection or other obvious pathology[1]. Overactive bladder, affecting a significant portion of the population[2,3] poses challenges due to its varied aetiologies and complex pathophysiology[4]. Therefore, understanding the correlation between treatment modalities and efficacy is crucial for optimizing therapeutic approaches and patient outcomes.

Current management recommendations for OAB encompass behavioural therapies, lifestyle modifications, pharmacological treatments (anticholinergics, β3-adrenergic receptor agonists), and surgical interventions, including minimally invasive therapies such as intra-vesical injections of botulinum toxina and sacral nerve modulation (SNM). However, the position of tibial nerve stimulation (TNS) within these therapeutic algorithms remains debated. According to the American Urological Association (AUA)[5] it should be considered as a third-line treatment, in the same way as SNM and intra-vesical injections of botulinum toxina. On the contrary, according to the European Association of Urology (EAU)[6] TNS can be offered as a first-line treatment or in case of failure of pharmacological treatments.

TNS consists of a unilateral electrical stimulation of the tibial nerve, a mixed nerve containing fibres issued from the L4 to S3 nerve roots. This stimulation can be performed percutaneously using a needle (PTNS), once or twice a week for 30 minutes per session, with a subjective and objective effectiveness of 61.4% and 60.6% respectively[7]. It can also be performed transcutaneously (TTNS), using adhesive electrodes, daily for 20 to 30 minutes per session with an improvement in symptoms reported in 48-93% of cases[8].

In case of failure or loss of efficacy, alternative therapies are recommended. Among minimally invasive surgical treatments, SNM has demonstrated effectiveness in managing OAB, with significant symptom improvement reported in 66% to 85% of cases[9,10]. SNM typically involves a two-stage implantation process, with a lead placed at the sacral root S3 level during the first procedure, followed by a test phase lasting 7 to 28 days to evaluate therapy effectiveness. If a 50% or greater improvement is observed, a definitive implantable pulse generator (IPG) is subcutaneously implanted during a second procedure. In the absence of established

predictive factors of efficacy[11] and despite a non-negligible complication rate of 16%[9,10] the test phase remains crucial.

Given that both TNS and SNM involve electrical stimulation of the S3 sacral fibres to modulate bladder function, it is plausible to consider that the efficacy of TNS may predict that of SNM. Although this hypothesis has been partially addressed in recent retrospective studies[12,13] it has only been evaluated in a small number of patients, all of whom had failed TTNS. It was therefore not possible to determine how the response to TTNS was correlated to the subsequent response to SNM.

The present study aims to evaluate whether the response to TTNS (success or failure) in OAB patients is correlated with the subsequent response to SNM. By investigating this correlation, we seek to provide valuable insights into the potential predictive value of TTNS for SNM outcomes.

METHODS

Study design

This retrospective study was conducted at two university hospital centers during the year 2022. The study protocol was registered with the French Advisory Committee on Information Processing in Material Research in the Field of Health (Commission Nationale Informatique et Liberté - CNIL) under the number DEC2022-278. All OAB patients, aged over 18-year-old, who received TTNS followed by a two-stage SNM between January 2016 and June 2022, were considered eligible. Overactive bladder was defined according to the terminology proposed by the ICS, including a complaint of urinary urgency, with or without urge urinary incontinence, increased daytime frequency or nocturia, in the absence of no proven infection or other obvious pathology[14]. Patients with isolated non-obstructive urinary retention (NOUR) or chronic pelvic pain syndrome (CPPS), and those who had previously undergone a SNM test phase before TTNS were excluded. However, patients presenting with OAB associated with voiding dysfunction (incomplete NOUR and/or slow urinary stream) were included when TTNS and SNM were proposed as an OAB treatment, and when voiding

dysfunction was considered mild or when previously managed (e.g., clean intermittent self-catheterization).

Transcutaneous tibial nerve stimulation

Tibial nerve stimulation was self-administered at home using the Urostim2® device (Schwa-Medico, Rouffach, France) and a couple of dedicated transcutaneous electrodes. Multichannel urodynamic study prior to TTNS initiation was not systematically performed but left to the discretion of the physician. Patients were prescribed the U3 program (10Hz, 200µs) for 20 minutes daily and were asked to discontinue any OAB medication (anticholinergic, β3-adrenergic agonist) prior to TTNS initiation. Similarly, in patients receiving intravesical injections of botulinum toxina, a wash-out period of 12 months was usually respected before TTNS initiation. Apart from potential contraindications (skin lesions, neuropathy, etc.), the choice of the side to stimulate was left to the patient's appreciation. After a dedicated therapeutic education consultation, the stimulator was left at the patient's disposal for 6 months, and a clinical re-evaluation was scheduled at 3 months. If significant improvement, assessed using a 3-day bladder diary and the Patient Global Impression of Improvement (PGI-I) scale, was observed at 3 months, the patient was provided with a final device to pursue the therapy.

Sacral nerve modulation

The Interstim II or Interstim Micro device (Medtronic, Minneapolis, MN, USA) was implanted through a two-stage procedure under general anaesthesia. Multichannel urodynamic study prior to SNM lead implantation was not systematically performed but left to the discretion of the physician. Patients were asked to discontinue any OAB medication (anticholinergic, β3-adrenergic agonist) prior to lead implantation - if initiated between TTNS and SNM. Similarly, in patients receiving intravesical injections of botulinum toxina, a wash-out period of 12 months was usually respected before SNM lead implantation. During the first step, the lead was implanted unilaterally at the S3 root, occasionally at S4, based on the best per-operative motor response. Polarity and amplitude were adjusted according to intraoperative motor and postoperative sensory responses, while frequency and pulse width were systematically set at

14 Hz and 210 µs, respectively. At the end of a 2 to 4-week test phase, if significant improvement was observed, assessed using a 3-day bladder diary and the PGI-I scale, the implantable pulsed generator (IPG) was permanently implanted during a second procedure. In case of failure, the lead was removed during this second procedure.

Outcomes of interest

The primary endpoint was the statistical correlation between the response (failure or success) to TTNS and the response (failure or success) to SNM. Success for both therapies was defined as a 50% or greater improvement in one or more bothersome lower urinary tract symptoms from baseline, as assessed using a 3-day bladder diary - including urinary urgency episodes, urinary incontinence episodes, daytime frequency and nocturia. Secondary endpoints included the statistical correlations between the response to TTNS and the response to SNM, while controlling for gender, age (<57 yo vs >57 yo), the presence or absence of an underlying neurological disease, and the presence or absence of detrusor overactivity (DO). Detrusor overactivity was defined according to the terminology proposed by the ICS as the occurrence of detrusor muscle contractions during filling cystometry[15].

Statistical analysis

Categorical variables are expressed as numbers (percentage). Continuous variables are expressed as means (standard deviation, SD) in the case of normal distribution or medians [range] otherwise. Normality of distribution is assessed using histograms and the Shapiro-Wilk test. To investigate whether the response to TTNS is predictive of the response to SNM in the overall population, we performed logistic regression. To study prediction in predefined populations (gender, age, underlying neurological disease and detrusor overactivity), we added the factor and interaction to the previous regression model. Odds ratios (ORs) are shown as measures of effect size, with their 95% confidence intervals (CIs). In addition, contingency tables are also constructed to observe the different frequencies between the two responses. Then, the evolution between urological parameters before and after TTNS, and before and after SNM are described. The evolution of these parameters according to clinical efficacy of TTNS, and then according to clinical efficacy of SNM, are compared using the Mann-

Whitney U test when numbers permitted. These analyses are performed in the overall population and in the gender, age, neurological and DO subpopulations. Statistical testing are done at the two-tailed α level of 0.05. Data are analyzed using SAS software package, release 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

Patients' characteristics

Out of the 291 patients who underwent a two-stage SNM between 2016 and 2022 at our two centers, 92 underwent both TTNS and subsequent SNM to treat OAB and were included in this study. The flowchart detailing the patient selection process is presented in Figure 1. At the time of TTNS initiation, there were 68 females (73.9%), and the median age was 57.0 [41.0-69.0] years. Sixteen patients (17.4%) presented a concomitant voiding dysfunction with OAB, with only one practicing clean self-intermittent catheterization. Among the 15 patients that were under spontaneous voiding, 11 (73.3%) underwent a multi-channel urodynamic before TTNS initiation, showing a median Qmax = 16.0 ml/s [13.0-21.0] and a median PVR volume = 0.0 ml [0.0;90.0]. Overall, multichannel urodynamic study was performed in 60 patients (65.2%) before TTNS initiation and in 57 patients (62.0%) before SNM lead implantation. Among them 34/60 (56.7%) and 38/57 (66.7%) had DO, respectively. Prior to TTNS, most patients had received pharmacological treatments, particularly anticholinergic medication (91.3%). A history of anti-incontinence surgery was present in 28 patients (30.4%), including 24 sub-urethral slings, 3 ACT® balloons, 6 artificial urinary sphincters, and 3 colposuspensions. Additionally, 24 patients (26.1%) had an underlying neurological disease, including brain lesions (3 patients), Parkinson's syndrome (7 patients), cerebral palsy (2 patients), surgical treatment for herniated disc (4 patients), chronic hydrocephalus (1 patient), and other diseases (7 patients). Patients' characteristics at baseline are presented in Table I.

Transcutaneous tibial nerve stimulation

The success of TTNS was observed in 22 patients (23.9%) after a median duration of use of 3.0 [3.0-4.5] months. Among the responders, a statistically significant decrease was observed in

the number of urgency episodes (median decrease = 5.0 [4.0-7.8] per 24 hours), daytime frequency (median decrease = 4.5 [3.3-5.0] per day), nocturia (median decrease = 2.0 [0.0-3.0] per night), and urinary incontinence episodes (median decrease = 0.0 [0.0-5.5] per 24 hours), compared to the non-responders. The evolution of the 3-day bladder diary parameters under TTNS is detailed in Table II. Based on the PGI-I scale, 6 patients (6.5%) reported being "improved" or "much improved", and 16 patients (17.4%) reported being "slightly improved". To note, all non-responders reported "no change", except one who reported to be "a little worse". Regarding the four patients that previously received intravesical injections of botulinum toxina, the median wash-out period since the last injection was 14 months [13-22]). Similarly, all medication for OAB were supposed to be discontinued before TTNS initiation.

Sacral nerve modulation

The median interval between discontinuation of TTNS and SNM test phase was 6.0 [4.0-11.0] months. The success of SNM was observed in 66 patients (71.7%) after a median test phase of 27.0 [16.0-29.0] days, leading to permanent implantation of an IPG. Most patients were implanted at the S3 sacral root level (97.8%), predominantly on the right side (73.6%). Like TTNS responders, significant reductions in the number of urgency episodes (median decrease = 6.0 [3.3-9.9] per 24 hours), daytime frequency (median decrease = 3.0 [2.0-5.0] per day), nocturia (median decrease = 2.0 [1.0-2.0] per night), and urinary incontinence episodes (median decrease = 4.0 [0.0-7.0] per 24 hours) were observed among SNM responders, compared to non-responders. The evolution of the 3-day bladder diary parameters under SNM is detailed in Table II. According to the PGI-I scale, 46 patients (40%) reported being "improved" or "much improved", and 20 patients (21.7%) reported being "slightly improved". To note, all non-responders reported "no change". Regarding the seven patients that received intravesical injections of botulinum toxina between TTNS discontinuation and SNM lead implantation, the median wash-out period since the last injection was 16.0 months [14.0-25.0]. Similarly, all medication for OAB were supposed to be discontinued before SNM lead implantation.

Outcomes of interest

Regarding the primary endpoint, there was no statistical correlation between the response to TTNS and the subsequent response to SNM, regardless of success or failure (95% CI [0.48 - 4.47], p = 0.51). After TTNS failure, SNM showed success in 49 out of 70 patients (70%), while after TTNS success, SNM showed success in 17 out of 22 patients (77.3%). Distribution of patients by response to TTNS and SNM is presented in Table III.

For the secondary endpoints, no statistical relationship was found between the response to TTNS and the response to SNM when controlling for age (<57 years old or ≥57 years old) with p-values of 1 and 0.69, respectively. Statistical analysis for other subgroups was limited by small sample sizes.

DISCUSSION

The current study aimed to investigate the predictive value of TTNS on the subsequent response to SNM in the treatment of OAB. Our findings revealed no statistical correlation between the response to TTNS and the response to subsequent SNM.

Although previous retrospective studies have partially explored this question, they were limited by a small number of patients, all of whom had previously failed TTNS[12,13]. Thus, the predictive value of the response to TTNS on the subsequent response to SNM could not be determined. To our knowledge, this study is the first to comprehensively investigate whether the response to TTNS (success of failure) can predict the response to SNM in the treatment of OAB.

The reported success rate of TTNS in this study (23.9%) was lower than what has been previously reported in the literature (48-93% of cases)[7,8]. However, caution should be exercised in interpreting this finding, as all patients eventually transitioned to SNM after TTNS, introducing a major selection bias. In contrast, the success rate reported for SNM (71.7%) can be more reliably interpreted and is comparable to previous studies, thus aligning our results with the existing literature (66% to 85% of cases)[9,10].

One possible explanation for the lack of statistical relationship between TTNS and SNM may lie in their different modes of administration. TTNS involved intermittent stimulation of the

tibial nerve at a frequency of 10 Hz and a pulse duration of 200 µs, delivered once daily for a 20-minute session. On the other hand, SNM provided direct and continuous stimulation to the sacral root at a frequency of 14 Hz and a pulse duration of 210 µs. Moreover, the underlying mechanisms of action for these two therapies remain unclear[16]. While SNM is thought to modulate spinal cord reflexes and brain networks through peripheral sensory and possibly motor neurons[17] the mechanism of action for TTNS is still not well-established. These are merely hypotheses, and we agree that comparing the mechanisms of action of TTNS and SNM remains a particularly hazardous exercise in view of the limited current knowledge in this field. Additionally, literature reports have highlighted anatomic variations in the branching pattern of both the sacral and tibial nerves[18] which could potentially contribute to modify correlation between TTNS and SNM.

Although percutaneous tibial nerve stimulation (PTNS) and TTNS have shown comparable results in the treatment of OAB[19], it is important to recognize that they are distinct therapies with differences in stimulation protocols, including mode of administration and stimulation parameters. Therefore, dedicated studies focusing on PTNS are warranted before extrapolating the results of this study to PTNS.

The present study, even if it can claim to provide preliminary data for research protocols with a higher level of evidence, has several limitations that need to be addressed. To begin with OAB concomitant treatments - even though it is important to remember that patients were systematically asked to discontinue their OAB medication (anticholinergic, β3-adrenergic agonist) before TTNS initiation and SNM lead implantation, we were unable to specify how long these treatments had been discontinued, or even whether they had been discontinued. The use of these drugs may have influenced the results of the TTNS and SNM and should therefore be considered a limitation. In addition, we noted that urodynamic parameters recorded in most of the 15 patients presenting with a voiding dysfunction were consistent with a mild dysfunction. Therefore, we hypothesized that voiding dysfunction did not significantly interfere with TTNS and SNM results in these patients and decided not to exclude them. This limitation should however be kept in mind when interpreting the results issued from the present study. Finally, among the 57 patients that presented with wet OAB, an unknown proportion had associated stress urinary incontinence. However, in view of our daily clinical practice, if patients were offered treatment for OAB - by TTNS and then by SNM - it

seems logical to us that urinary urgency was their main functional complaint. It is therefore unlikely that this lack of data will have a significant impact on the results of the study, particularly as regards the correlation between the efficacy of TTNS and SNM - considered as two treatments for OAB.

CONCLUSION

Despite the questions raised and the limitations associated with its retrospective design, this study provides valuable insights for better informing the treatment decision process for OAB patients. It highlights that TTNS and SNM should be considered as two separate therapies, with the response to TTNS not predicting the response to SNM.

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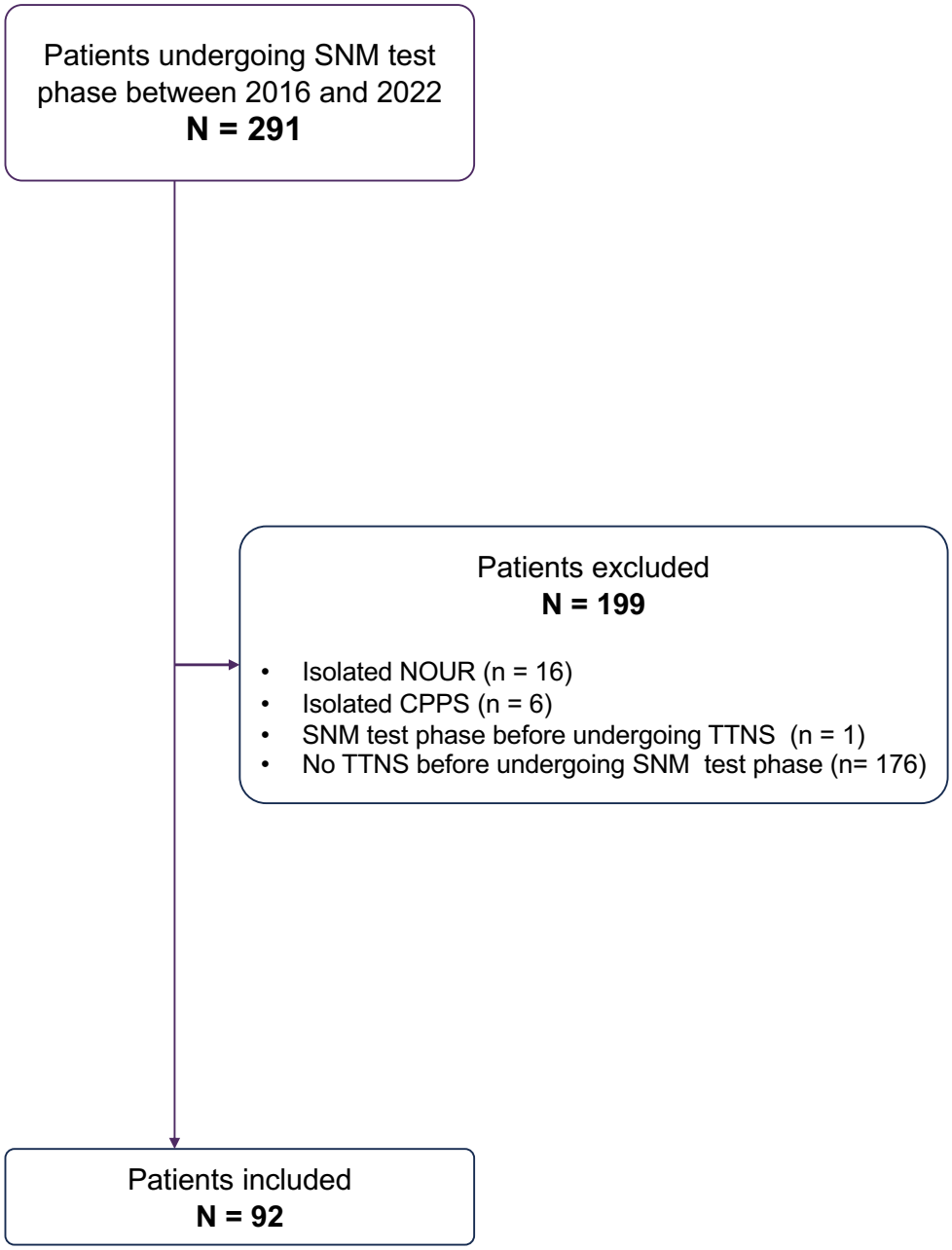
Figure 1: Flowchart detailing the patient selection process



SNM: sacral nerve modulation; **TTNS:** Transcutaneous tibial nerve stimulation; **NOUR:** Nonobstructive urinary retention; **CPPS:** Chronic pelvic pain syndrome

Table I: Patients' characteristics

	N = 92	
Age (years**)**		
At the time of TTNS (median ［Q1 - Q3］)	57.0	[41.0-69.0]
At the time of SNM (median ［Q1 - Q3］)	60.5	[44.0-72.5]
Gender		
Female	68	73.9%
Male	24	6.1%
BMI (kg/m^2) At the time of TTNS (median ［Q1 - Q3］)	26.3	[22.8-30.5]
LUTS At the time of TTNS		
Pure OAB	**76**	**82.6%**
Dry OAB	14	18.4%
Wet OAB	57	75.0%
Unknown	5	5.4%
OAB associated with voiding dysfunction	**16**	**17.4%**
Dry OAB	9	9.8%
Wet OAB	6	6.5%
Unknown	1	1.1%
Multi-channel urodynamic study		
At the time of TTNS	**60**	**65.2%**
First sensation of filling (mL) (median ［Q1 - Q3］)	145.0	[102.5-225.5]
Maximal cystomanometric capacity (mL) (median ［Q1 - Q3］)	270.0	[178.0-350.0]
Detrusor overactivity	34	56.7%
Volume at first inhibited detrusor contraction (mL) (median ［Q1 - Q3］)	194.5	[120.3-269.5]
Maximal detrusor pressure (cmH_2O) (median ［Q1 - Q3］)	68.0	[53.0-77.0]
At the time of SNM	**57**	**62.0%**
First sensation of filling (mL) (median ［Q1 - Q3］)	145.0	[70.0-182.0]
Maximal cystomanometric capacity (mL) (median ［Q1 - Q3］)	190.0	[141.0-330.0]
Detrusor overactivity	38	66.7%
Volume at first inhibited detrusor contraction (mL) (median ［Q1 - Q3］))	131.0	[83.0-196.0]
Maximal detrusor pressure (cmH_2O) (median ［Q1 - Q3］)	62.	[47.0-76.0]
Underlying neurological disease	24	26.1%
Duration of symptoms before TTNS (years) (median ［Q1 - Q3］)	2.0	[1.0-7.0]
Pharmacological treatments initiated before TTNS		
Alpha blocker	12	13.0%
Anticholinergic	84	91.3%
β3-drenergic agonist	5	5.4%
Intravesical injections of Botulinum toxina	4	4.3%
Pharmacological treatments initiated between TTNS and SNM		
Alpha blocker	1	1.1%
Anticholinergic	21	22.8%
β3-adrenergic agonist	9	9.8%
Intravesical injections of Botulinum toxina	7	7.8%

Values are presented as frequency (percentage) unless otherwise indicated.

BMI: Body mass index; **LUTS:** Lower urinary tract symptoms**; OAB**: Overactive bladder
TTNS: Transcutaneous tibial nerve stimulation; **SNM**: Sacral nerve modulation

Table II: Evolution of the 3-day bladder diary parameters under TTNS and SNM

	TTNS							SNM						
	Baseline		End of test phase		Decrease		p-value	Baseline		End of test phase		Decrease		p-value
Urinary urgency episodes *(per 24h)*														
Overall	**9.0**	**[6.8-12.3]**	**8.0**	**[4.8-10.3]**	**0.0**	**[0.0-1.0]**		**9.0**	**[5.0-13.0]**	**3.0**	**[1.0-6.0]**	**5.0**	**[1.0-8.0]**	
Responders	10.0	[8-12.3]	4.5	[3.0;5.8]	5.0	[4.0-7.8]	<.0001	9.0	[7.0-12.0]	3.0	[1.0-4.8.0]	6.0	[3.3-9.0]	<.0001
Non-responders	8.5	[6-10]	8.5	[5.3;13.5]	0.0	[0.0-0.0]		8.0	[2.5-14.0]	5.0	[2.0-9.0]	0.0	[0.0-2.0]	
Daytime frequency *(per day)*														
Overall	**9.0**	**[7.3-10.8]**	**8.5**	**[7.0;10.0]**	**0.0**	**[0.0-1.0]**		**9.0**	**[7.0-11.8]**	**6.5**	**[5.0-8.0]**	**2.5**	**[0.0-4.0]**	
Responders	10.0	[10.0-11.5]	6.0	[5.0;6.8]	4.5	[3.3-5.0]	<.0001	9.0	[7.0-12.0]	6.0	[5.0-8.0]	3.0	[2.0-5.0]	0.0002
Non-responders	9.0	[7.0-10.3]	9.0	[7.0;11.0]	0.0	[0.0-0.0]		9.0	[7.0;10.0]	8.0	[6.0-12.0]	0.0	[0.0-1.0]	
Nocturia *(per night)*														
Overall	**2.0**	**[1.0-4.0]**	**2.0**	**[1.0-3.0]**	**0.0**	**[0.0-1.0]**		**2.0**	**[2.0-4.0]**	**1.0**	**[0.0-2.0]**	**1.0**	**[0.0-2.0]**	
Responders	2.5	[0.8-4.0]	1.0	[0.8-1.3]	2.0	[0.0-3.0]	0.0077	2.0	[2.0-3.0]	1.0	[0.0-1.0]	2.0	[1.0-2.0]	0.0062
Non-responders	2.0	[1.0-4.0]	2.0	[1.0-4.0]	0.0	[0.0-0.0]		2.5	[0.8-5.3]	1.5	[0.8-3.3]	0.0	[0.0-1.3]	
Urinary incontinence episodes *(per 24h)* *n = 57*														
Overall	**2.0**	**[0.0-7.0]**	**1.5**	**[0.0-6.0]**	**0.0**	**[0.0;0.0]**		**3.0**	**[0.0-8.5]**	**0.0**	**[0.0-3.0]**	**0.0**	**[0.0-5.0]**	
Responders	7.0	[0.0-8.0]	0.0	[0.0-2.5]	0.0	[0.0-5.5]	0.0005	5.0	[0.0-9.0]	1.0	[0.0-3.0]	4.0	[0.0-7.0]	<.0001
Non-responders	2.0	[0.0-6.8]	2.5	[0.0-7.8]	0.0	[0.0-0.0]		0.0	[0.0-2.8]	0.0	[0.0-2.8]	0.0	[0.0-0.0]	

Values are presented as median [IQR1-IQR3].

TTNS: Transcutaneous tibial nerve stimulation; **SNM**: Sacral nerve modulation

Table III: Distribution of patients by response to TTNS and SNM

		TTNS		
		Responders	Non responders	Overall
SNM	Responders	77.3%	70.0%	71.7%
	Non responders	22.7%	30.0%	28.3%
	Overall	23.9%	76.1%	100.0%

TTNS: Transcutaneous tibial nerve stimulation; **SNM**: Sacral nerve modulation

DEVELOPMENT OF A PREDICTIVE TOOL FOR SACRAL NERVE MODULATION IMPLANTATION IN THE TREATMENT OF NON-OBSTRUCTIVE URINARY RETENTION AND/OR SLOW URINARY STREAM - A STUDY FROM THE NEURO-UROLOGY COMMITTEE OF THE FRENCH ASSOCIATION OF UROLOGY

Thirdly, we questioned the possibility of developing predictive tools, particularly in the context of voiding dysfunction. In this indication, the sacral neuromodulation success rate is highly variable, ranging from 33% to 100% depending on the study.

Having such predictive tools at our disposal could enable us to better support our patients in the medical decision making process.

These results could also help us understand the mechanisms of action of sacral neuromodulation as a treatment for voiding dysfunction.

The retrospective work presented below was published in the *World Journal Of Urology* in 2023 (157).

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ABSTRACT

Purpose: To seek predictive factors and develop a predictive tool for sacral nerve modulation (SNM) implantation in patients with non-obstructive urinary retention and/or slow urinary stream (NOUR/SS).

Methods: It was designed as a retrospective study including all patients who have undergone a two-stage SNM for NOUR/SS between 2000-2021 in 11 academic hospitals. The primary outcome was defined as the implantation rate. Secondary outcomes included changes in bladder emptying parameters. Univariate and multivariable logistic regression analysis were performed and determined odds ratio for IPG implantation to build a predictive tool. The performance of the multivariable model discrimination was evaluated using the c-statistics and an internal validation was performed using bootstrap resampling.

Results: Of the 357 patients included, 210 (58.8%) were finally implanted. After multivariable logistic regression, 4 predictive factors were found, including age (≤52 yo; OR =$3.31_{CI95\%}$[1.79; 6.14]), gender (female; OR=$2.62_{CI95\%}$[1.39; 4.92]), maximal urethral closure pressure (≥70 cmH_2O; OR: $2.36_{CI95\%}$[1.17; 4.74]) and the absence of an underlying neurological disease affecting the lower motor neuron (OR =$2.25_{CI95\%}$[1.07; 4.76]). Combining these factors, we established 16 response profiles with distinct IPG implantation rates, ranging from 8.7% to 81.5%. Internal validation found a good discrimination value (c-statistic, 0.724; 95%CI, 0.660 to 0.789) with a low optimism bias (0.013). This allowed us to develop a predictive tool (https://predictivetool.wixsite.com/void).

Conclusion: The present study identified 4 predictive factors, allowing to develop a predictive tool for SNM implantation in NOUR/SS patients, that may help in guiding therapeutic decision-making. External validation of the tool is warranted.

INTRODUCTION

Non-obstructive urinary retention and/or slow urinary stream (NOUR/SS) can be likened to the concept of voiding dysfunction as defined by the International Continence Society as an abnormally slow and/or incomplete emptying, based on an abnormally slow urine flow rate and/or an abnormally high post-void residual (1,2). This condition may or may not be associated with neurological disease and represents a significant health issue, affecting up to 9-48% of men and 12-45% of women (3).

Because clean intermittent self-catheterization (CISC) stands as the standard of care to restore normal bladder emptying (4) NOUR/SS can sometimes be considered as a challenging condition. Indeed, although CISC is associated with a low rate of complications and most patients report competence and confidence in performing CISC, many feel embarrassed and express apprehension about potential long-term adverse effects (5).

Since 1988 and following the pioneering work of Tanagho and Schmidt (6) sacral nerve modulation (SNM) has gradually emerged as a viable therapeutic option in the management of NOUR/SS (7). However, despite the identification of some predictive factors that may influence the outcome of SNM, the optimal indications for SNM in the NOUR/SS population remain unclear (7) and predictive tools have yet to be developed (8). With a success rate varying between 33% and 100%, during a median follow-up going from 6 to 60 months (9-11) the development of a predictive tool would be valuable for guiding therapeutic decision-making by identifying candidates with the highest likelihood of SNM success.

The present study aimed to seek predictive factors and to develop a predictive tool for SNM implantation in patients with NOUR/SS.

METHODS

Study design

The present study was designed as a retrospective multicenter study conducted at 11 academic hospitals in France. The protocol has been declared to the French Advisory Committee on Information Processing in Material Research in the Field of Health (Commission Nationale Informatique et Liberté - CNIL) under the number DEC21-242. The study included all patients who underwent a two-stage SNM for the treatment of NOUR/SS between 2000 - 2021, including patients with "complete urinary retention", "incomplete urinary retention" and "impaired uroflowmetry without significant post-void residual volume".

Sacral nerve modulation implantation

The InterStim and InterStim II™ systems (Medtronic, Minneapolis, MN, USA), consisting of a neurostimulator and a quadripolar tined lead, were used in the 11 participating centers. All patients underwent a two-stage SNM procedure (12). In the first stage, the lead was unilaterally or bilaterally implanted under fluoroscopic guidance. The lead was then connected to an external electrical generator, and a test phase lasting 7 to 28 days was conducted to assess improvement in NOUR/SS. If the patient showed significant improvement (50% or greater), an implantable pulse generator (IPG) was implanted during a second surgery.

Outcomes of interest

The primary outcome was defined as the IPG implantation. Secondary outcomes included changes in maximum urine flow rate (Qmax), post-void residual (PVR) volume, and bladder voiding efficiency (BVE) ratio between baseline and the end of the test phase.

Statistical analysis

Categorical variables are reported as frequency (percentage). Quantitative variables are reported as mean (standard deviation, SD) in the case of normal distribution or median

(interquartile range, IQR) otherwise. Normality of distributions was assessed using histograms and using the Shapiro-Wilk test.

Associations between patient characteristics and SNM implantation were evaluated using a generalized linear mixed model (GLMM, with binary distribution and logit link function) with center as random effect to account for the potential site effect. For quantitative variables, the log-linearity assumption was checked by using restricted cubic spline functions (13). For quantitative variables significantly associated with SNM implantation, we determined the optimal threshold to predict SNM implantation by maximizing the Youden index from Receiver Operator Characteristic (ROC) curves to provide a simple prognostic tool. All patient characteristics significantly associated in bivariate analysis ($P<0.05$) were then introduced into a multivariable GLMM to provide the prognostic tool. Odd-ratios (ORs) of SNM implantation with theirs 95% confidence interval (CI) were derived for each independent predictors as the effect size measures. The performance of the multivariable model discrimination (which indicates to what extent the model distinguishes between patients with SNM implantation from those without) was evaluated using the c-statistics and an internal validation was performed using bootstrap resampling with 200 repetitions to quantify the over-optimism bias. The multivariable prognostic model was fitted after excluding firstly patients with "impaired uroflowmetry without significant PVR volume" and secondly patients with bilateral lead implantation, as sensitivity analysis. All statistical tests were done at the two-tailed α-level of 0.05 using the SAS software version 9.4 (SAS Institute, Cary, NC).

RESULTS

Patients' characteristics

A total of 357 patients were included, with a majority being female (67.2%) and a median age of 45.1 years (IQR 32.8; 59.2). Most patients (62.6%) were under CISC, either exclusively or in combination with spontaneous voiding (Table 1). Almost half of the patients (43.1%) had an underlying neurological disease, with 78 (21.8%) affecting the upper motor neuron (UMN) and 72 (20.2%) affecting the lower motor neuron (LMN) (Supplementary Table 1).

Predictive factors for IPG implantation

Two-hundred and ten (58.8%) patients were implanted after a median test phase of 17 days (IQR 14; 28). The results of the univariate analysis, covering 17 potential predictors, are presented in Table 2. After multivariable analysis, gender - "*female*" versus *"male"* - (OR 2.62 [95%CI 1.39; 4.92]; p=0.003), age - *"*≤52 *year-old"* versus *">52 year-old"* - (OR 3.31 [95%CI 1.79; 6.14]; p<0.001), underlying neurological disease - *"no underlying neurological disease" and "neurological disease affecting the UMN"* versus *"neurological disease affecting the LMN"* - (OR 2.25 [95%CI 1.07; 4.76]; p=0.033) and maximal urethral closure pressure (MUCP) *"≥70cmH_2 O"* versus *"<70cmH_2 O"* (OR 2.36 [95%CI 1.17; 4.74]; p=0.016) appeared as independent predictive factors for IPG implantation. Similar results were found after excluding patients with "impaired uroflowmetry without significant PVR volume" (n=31, Supplementary Table 2) and patients with bilateral lead implantation (n= 29, Supplementary Table 3).

Developing a predictive tool

Combining these 4 predictive factors, we established 16 response profiles with distinct IPG implantation rates, ranging from 8.7% - for the most unfavorable combination - to 81.5% for the most favorable combination (Supplementary Figure 1). Internal validation using bootstrapping techniques found a good discrimination value (c-statistic, 0.724; 95%CI, 0.660 to 0.789) with a low optimism bias (0.013) (Supplementary Figure 2).This allowed us to develop a predictive tool, named VOID and made available as a downloadable Excel sheet, to easily assess the expected IPG implantation rate (with 95% confidence interval) in the context of NOUR/SS (Supplementary Figure 3).

Changes in bladder emptying parameters

Considering implanted patients, Q_{max} increased from 11 ml/s (IQR 6.8; 16.0) to 17.5 ml/s (IQR 13.0; 25.0) ($p < 0.001$) while PVR volume decreased from 200 ml (IQR 79.5; 307.5) to 28 ml (IQR 0.0; 90.0) ($p < 0.001$) and BVE ratio increased from 40.2% (IQR 15.8; 75.3) to 87.6% (IQR 72.5; 100) ($p < 0.001$). Considering non-implanted patients, Q_{max} remained at 10 ml/s (IQR 6.0; 15.1) - *versus* 10 ml/s (IQR 6.3; 15.0) at baseline ($p = 0.68$), while PVR volume increased

from 209.5 ml (IQR 90.0; 373.0) to 230 ml (IQR 154.0; 310.0) (p = 0.68) and BVE ratio decreased from 45.4% (IQR 15.7; 67.0) to 39.2% (IQR 21.1; 58.1) (p = 0.46).

DISCUSSION

In the era of personalized medicine, it seems essential to develop predictive tools that could be easily used in our daily clinical practice. Indeed, even if considered as an alternative therapy to CISC (7), SNM has been reported to significantly improve NOUR/SS within a range going from 33% to 100% (9) meaning that it will not work for everyone. Being able to select the best candidates for SNM could help us to better support our patients in their treatment decision-making. Based on these needs, we developed an innovative multivariate predictive tool for IPG implantation in the context of NOUR/SS, combining 3 clinical parameters and 1 urodynamic parameter. Since "slow urinary stream without significant PVR volume" is not considered an indication of SNM in some health care systems, and bilateral electrode implantation is far from being established as a standard practice, it seemed interesting to us to test our predictive tool by excluding these patients. Excluding these two questionable populations, our 4 predictive factors remained valid after multivariate analysis.

We reported here an IPG implantation rate of 58.8%, consistent with two recent meta-analysis reporting a mean IPG implantation rate going from 54.2% to 79.2% in NOUR/SS (10,14). Furthermore, the four predictive factors we identified have all been previously reported separately in the context of NOUR and/or overactive bladder (OAB).

As a first predictive factor, we reported a significant advantage for female. In a recent systematic review, Jairam et *al.* (8) reported that 7 studies, including OAB and NOUR patients, found a higher chance of IPG implantation in female. For some authors, this advantage of women over men could be explained by differences in central micturition regulation and sex hormones, postulated to account for differences in lower urinary tract function between genders (15). In our opinion, anatomical and functional differences of the urethral tract associated with an underdiagnosis of bladder outlet obstruction (BOO) in relation to benign prostatic hypertrophy (BPH) in males could also be implicated in these poorer results. This is well illustrated by the results reported by Coolen et *al.* (16) who showed that previous

transurethral resection of the prostate (TURP) and/or bladder neck incision (BNI) (OR 7.71, 95% CI: 1.43-41.5) were significant predictors of SNM success.

As a second predictive factor, we reported a significant advantage for younger patients, under 52 years old. Jairam et *al.* (8) reported a higher success rate in patients under 43 years old (17). Similarly, in a more recent study including NOUR patients (13 men, 39 women), Al Hashimi et *al*. (18) reported age as the only factor being statistically associated with IPG implantation, with an optimal age very close to the one we reported, under 58.5 years. Interestingly, High et *al*. (19) reported that increased decade of age was associated with reduced implantation in all NOUR patients [OR 0.54 (95% CI 0.42, 0.70)]. This advantage of younger over older patients could be partly explained by differences in the etiopathogenesis underlying NOUR. Indeed, as underactive bladder is generally age-related, its prevalence increases in older patients (20). Jairam et *al*. (8) explored this crucial point and reported that NOUR patients with a reduced detrusor contractility had a lower rate of IPG implantation. In addition to the higher prevalence of underactive bladder, it may be added the higher prevalence of BPH in older male patients, which may be underdiagnosed in some NOUR patients undergoing SNM.

As a third predictive factor, we identified the presence of an underlying neurological disease affecting LMN to negatively impact IPG implantation rate. Interestingly, Panicker et *al*. (21) stated as a conclusion of a recent review that "it [was] still unclear which neurological patients [were] most suitable for [SNM]". The present results, along with some data issued from women with deep pelvic endometriosis (DPE), may provide a beginning of answer. Indeed, even if DPE is not a neurological disease, it is often responsible for pelvic nerve damage, and is therefore an interesting model - even not perfect - of disease affecting LMN. Nyangoh Timoh et *al.* (22) and Agnello et *al.* (23) reported a low improvement rate of NOUR in this specific population (15.4%-40.0%). Furthermore, it is important to remember that patients with an underlying disease affecting LMN often have detrusor under- or acontractility as a urodynamic consequence (21) which has been reported to be associated with a lower SNM success rate.

Finally, as a unique urodynamic predictive factor, we identified MUCP≥70cmH_2 O to be statistically associated with IPG implantation. Although rarely reported in the literature,

similar results have been previously presented by Game et *al*. (24) during International Continence Society (ICS) meeting. They found that IPG implantation rate was higher in patients with urethral sphincter electromyography abnormalities consistent with a primary disorder of sphincter relaxation. They also reported that mid-term SNM success rate was higher in patients with a high MUCP. As Game et *al*. (24) we think that patients with a high MUCP probably have a primary disorder of sphincter relaxation, on which SNM would be more efficient. As reminded by De Wachter et *al.* (25) in a recent review, an overactive urethra generates abnormally strong inhibitory afferent signals that block bladder afferent activity at the sacral level and deactivate the periaqueductal grey and higher centers resulting in loss of bladder sensation and NOUR.

Interestingly, univariate analysis showed that patients implanted with IPG tended to have a lower stimulation amplitude at the time of lead placement, even if not statistically significant. To focus on predictive factors related to patients, we initially wondered whether to exclude patients with a stimulation amplitude over than 2 mA. Because they were very few (3.6%), we finally decided not to exclude them from the analysis.

Here, we focused on the IPG implantation rate. We made this choice because of the lack of consensus that currently exists on what is a success when considering SNM as a treatment of NOUR. Even if the historical "50%" rule is often respected, no author agrees on what this "50%" means. This is well illustrated by Ho et *al*. (10) in a recent review, stating that "test-stimulation success varied considerably across all the [...] studies". Because the choice to implant IPG is often a shared decision between the physician and the patient, and because the present study includes 357 patients in 11 different academic centers, we believe that the IPG implantation rate should be, even if not exactly similar, at least partially correlated with the success rate. This is well corroborated by the significant improvement we reported in bladder emptying parameters in implanted patients.

While our study provides valuable insights into the efficacy of SNM in the treatment of NOUR/SS, there are several limitations that must be acknowledged. For instance, we did not gather data on prior or current BPH treatments in men. Furthermore, even if all patients underwent a cystometry associated with a urethral profilometry, only a small proportion of

patients underwent a pressure-flow study during their initial assessment. This exam would have given us interesting information on detrusor contractility. Finally, we were not able to describe device setting strategies nor the precise duration of the test phase and analyze their impact on the present predictive tool.

To help practitioners to explore personalized medicine and to test our predictive tool, we have developed a website where an Excel sheet can be downloaded (https://predictivetool.wixsite.com/void). Nonetheless, in the absence of any external validation, it cannot be advised to use the present predictive tool in daily clinical practice. External validation will be the subject of future scientific works.

CONCLUSION

Age, gender, underlying disease affecting LMN and MUCP were significant predictive factors for IPG implantation in NOUR/SS patients. We developed an easy-to-use predictive tool based to help in treatment decision-making.

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Table 1: Patients' characteristics at baseline

Age (years), *median (IQR)*	45.1	(32.8; 59.2)
BMI (kg/m^2), *median (IQR)*	23.7	(20.7; 27.6)
Gender		
Men	117	32.8%
Women	240	67.2%
Underlying neurological disease	154	43.1%
Vaginal prolapse	**28**	**11.7%**
Anterior	16	6.7%
Posterior	4	1.7%
Anterior + posterior	8	3.3%
History of stress urinary incontinence surgery	**31**	**9.7%**
Mid-urethral sling	27	7.6%
ACT balloons	1	0.3%
Artificial urinary sphincter	1	0.3%
Colposuspension	6	1.7%
History of vaginal prolapse surgery*.	**14**	**5.8%**
Sacrocolpopexy	6	2.5%
Vaginal repair	8	3.3%
Voiding mode		
Spontaneous voiding	193	54.7%
Reflex voiding	14	4.0%
CISC**	221	62.6%
Third-person catheterization	22	6.2%
Suprapubic catheter	10	2.8%
Indwelling urethral catheter	17	4.8%
Voiding capacity		
Complete urinary retention	120	33.6%
Incomplete urinary retention	206	57.7%
Impaired uroflowmetry without significant PVR volume	31	8.7%
Duration of symptoms (years) *median (IQR)*	3.0	(2.0; 6.0)
Urodynamic parameters		
Qmax (ml/s), *median (IQR)*	10.5	(6.8; 15.5)
PVR (ml), *median (IQR)*	200.0	(88.5; 340.0)
Maximal cystometric capacity, *median (IQR*)	500.0	(360.0; 600.0)
Detrusor overactivity	49	13.7%
MUCP (cmH_2O), *median (IQR)*	87.0	(70.0; 113.5)

Values are presented as frequency (percentage), unless otherwise indicated.

* Considering only female population; **: exclusively or in combination with spontaneous voiding;

IQR: interquartile range; **BMI:** body mass index; **CISC**: clean intermittent self-catheterization; **PVR**: post-void residual volume; **MUCP**: maximal urethral closure pressure

Table 2: Predictive factors for IPG implantation (univariate analysis)

	No IPG location N = 147		IPG Implantation N = 210		p value
Epidemiological					
Gender					
Men	57	38.8%	60	28.6%	**0.02***
Women	90	61.2%	150	71.4%	
Age (years), *median (IQR)*	51.7	(39.0; 66.6)	42.1	(27.1; 50.9)	**< 0.001***
Clinical					
BMI (kg/m^2), *median (IQR)*	24.2	(21.5; 28.4)	23.2	(20.3; 27.4)	0.21
Vaginal prolapse	12	13.3%	20	13.4%	0.94
Duration of symptoms (years), *median (IQR)*	3.0	(2.0; 5.0)	3.0	(1.7; 6.0)	0.67
On-going medications affecting bladder contractility	43	29.2%	62	29.5%	0.44
Urodynamic					
Voiding capacity					
Complete urinary retention	53	36.1%	67	31.9%	
Incomplete emptying	85	57.8%	121	57.6%	0.09
Impaired uroflowmetry without significant PVR volume	9	6.1%	22	10.5%	
Q_{max} (ml/s), *median (IQR)*	10.0	(6.3; 15.0)	11.0	(6.8; 16.0)	0.48
PVR (ml), *median (IQR)*	209.5	(90.0; 373.0)	200.0	(79.5; 307.5)	0.30
Detrusor overactivity	29	19.7%	20	9.5%	0.12
Maximal cystometric capacity, *median (IQR*)	500.0	(382.0; 600.0)	500.0	(353.0; 654.5)	0.11
MUCP (cmH2O), *median (IQR)*	80.0	(57.0; 108.0)	90.5	(75.0; 120.0)	**0.001***
Medical history					
Underlying neurological disease					
No neurological disease	80	54.4%	129	61.4%	
UMN	29	19.7%	47	22.4%	0.058
LMN	38	25.9%	34	16.2%	
No neurological disease + UMN	110	74.8%	176	83.8%	**0.02***
LMN	37	25.2%	34	16.2%	
Surgical history					
Stress urinary incontinence surgery	10	7.1%	21	11.7%	0.13
SNM-related factors					
Type of lead implantation					
Unilateral	133	90.5%	195	92.9%	0.11
Bilateral	14	9.5%	15	7.1%	
Amplitude (mA), *median (IQR*)	1.1	(0.7; 2.0)	0.8	(0.6; 1.4)	0.07
Pulse rate (Hz), *mean ± SD*	14.2	± 9.0	16.1	± 8.4	0.70

Values are presented as frequency (percentage), unless otherwise indicated.

IPG: implantable pulse generator; **IQR**: interquartile range**; BMI:** body mass index; **UMN**: upper motor neuron; **LMN**: lower motor neuron; **SUI**: stress urinary incontinence; Q_{max} : maximal uroflow; **PVR**: post-volume residual; **MUCP:** maximal urethral closure pressure; **SD**: standard deviation

* Considering only female population

Multiple sclerosis, incomplete spinal cord injury, Parkinson's disease, brain injury and cerebral palsy were considered as affecting the upper motor neuron (UMN). Incomplete cauda equina syndrome, pelvic surgery (rectal and deep pelvic endometriosis) and diabetes mellitus were considered as affecting the lower motor neuron (LMN). Fowler's syndrome was not considered as a neurological disease. Since in spina bifida patients, UMN and LMN are often both affected, we decided not to include them when comparing neurological diseases affecting UMN or LMN.

Supplementary Table 1: Underlying neurological disease

	N	%
Neurological disease affecting the UMN	**78**	**21.8%**
Brain injury	21	5.9%
Vascular	*12*	*3.4%*
Traumatic	*2*	*0.6%*
Congenital	*7*	*2.0%*
Multiple sclerosis	20	5.6%
Incomplete spinal cord injury	19	5.3%
Cerebral palsy	7	2.0%
Parkinson's disease	7	2.0%
Spina bifida	4	1.1%
Neurological disease affecting the LMN	**72**	**20.2%**
Pelvic surgery	34	9.5%
Rectal	*6*	*1.7%*
Endometriosis	*13*	*3.6%*
Others	*16*	*4.5%*
Incomplete cauda equina syndrome	26	7.3%
Diabetes mellitus	8	2.2%
Spina bifida	4	1.1%
Others	8	2.2%

Values are presented as frequency (percentage).

UMN: Upper motor neuron; **LMN:** Lower motor neuron

*Spina bifida patients are presented twice in this table, as having an underlying neurological disease affecting the UMN and the LMN.

Fowler's syndrome was not considered as a neurological disease.

Supplementary Table 2: Multivariate analysis of independent predictors of IPG implantation, overall and in sensitivity analysis after excluding patients with "impaired uroflowmetry without significant PVR volume**".**

	Main analysis		**Sensitivity analysis**	
	OR (95%CI)	p	OR (95%CI)	p
Age, ≤52 vs.>52 years	3.31 (1.79 to 6.14)	<0.001	3.34 (1.74 to 6.41)	<0.001
Gender, female vs. male	2.62 (1.39 to 4.92)	0.003	2.60 (1.31 to 5.13)	0.006
Maximal MUCP≥70 vs. <70 cmH2	2.36 (1.17 to 4.74)	0.016	2.07 (0.99 to 4.29)	0.051
Underlying neurological disease affecting LMN, absence vs. presence	2.25 (1.07 to 4.76)	0.033	2.33 (1.04 to 5.22)	0.039
C-statistics	*0.724 (0.660 to 0.789)*		*0.721 (0.653 to 0.789)*	

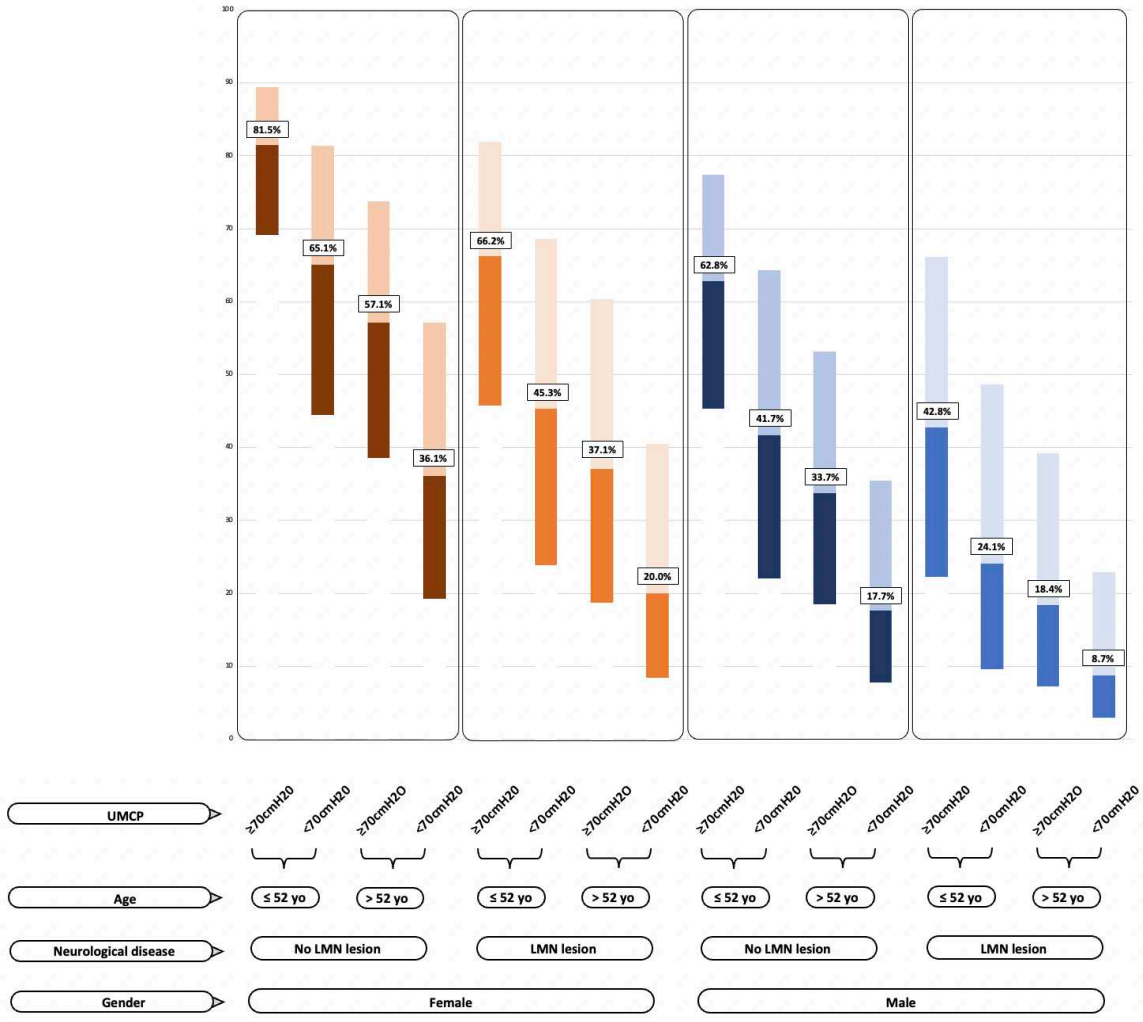
LMN: lower motor neuron; **PVR**: post-volume residual; **MUCP**: maximal urethral closure pressure; **OR**: odds ratio; **CI**: confidence interval

Supplementary Table 3: Multivariate analysis of independent predictors of IPG implantation after excluding patients with bilateral lead implantation

	OR (95%CI)	p
Age, ≤52 vs.>52 years	4.68 (2.31 to 9.46)	<0.001
Gender, female vs. male	2.06 (1.00 to 4.21)	0.047
Maximal MUCP≥70 vs.<70 cmH2	2.75 (1.26 to 6.01)	0.011
Underlying neurological disease affecting LMN, absence vs. presence	2.81 (1.20 to 6.57)	0.018
C-statistics	*0.754 (0.686 to 0.821)*	

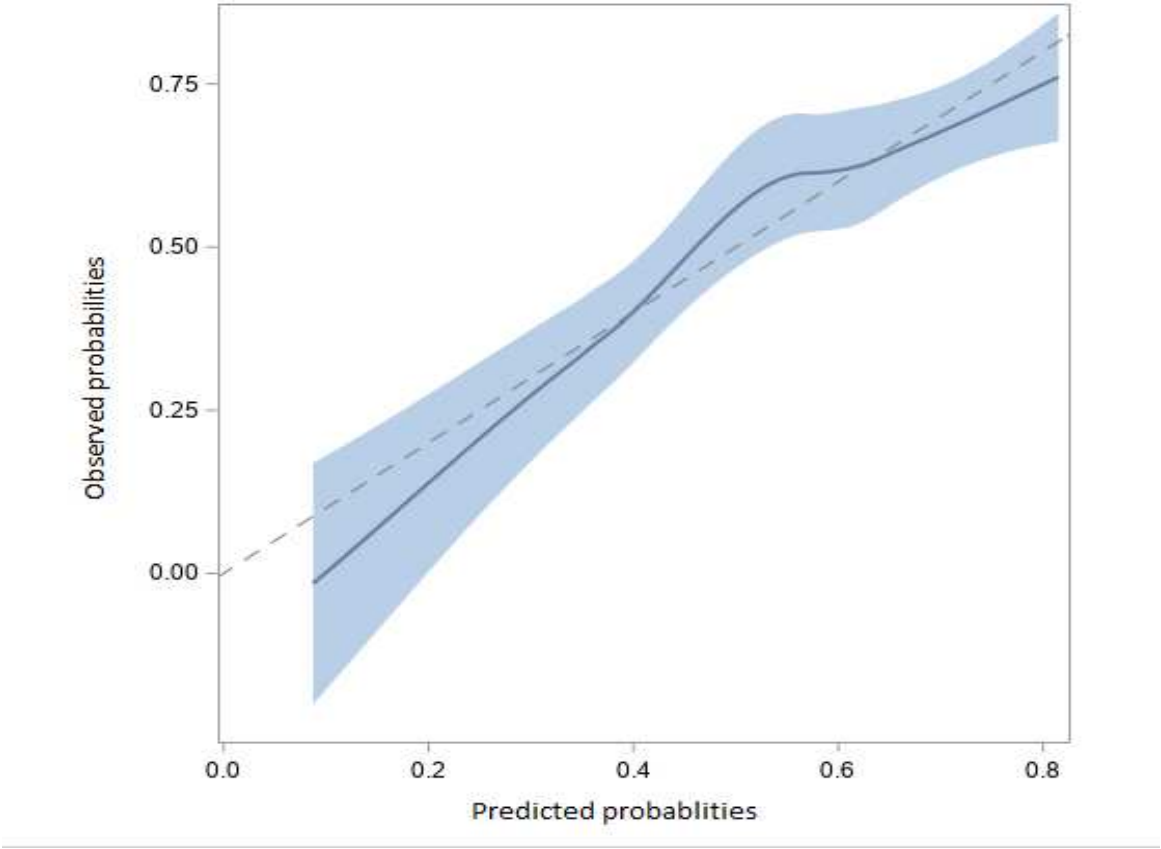
LMN: lower motor neuron; **PVR**: post-volume residual; **MUCP**: maximal urethral closure pressure; **OR**: odds ratio; **CI**: confidence interval

Supplementary Figure 1: IPG implantation rate (with 95% confidence interval) for the 16 profiles obtained from the combination of the 4 predictive factors identified in multivariate analysis.



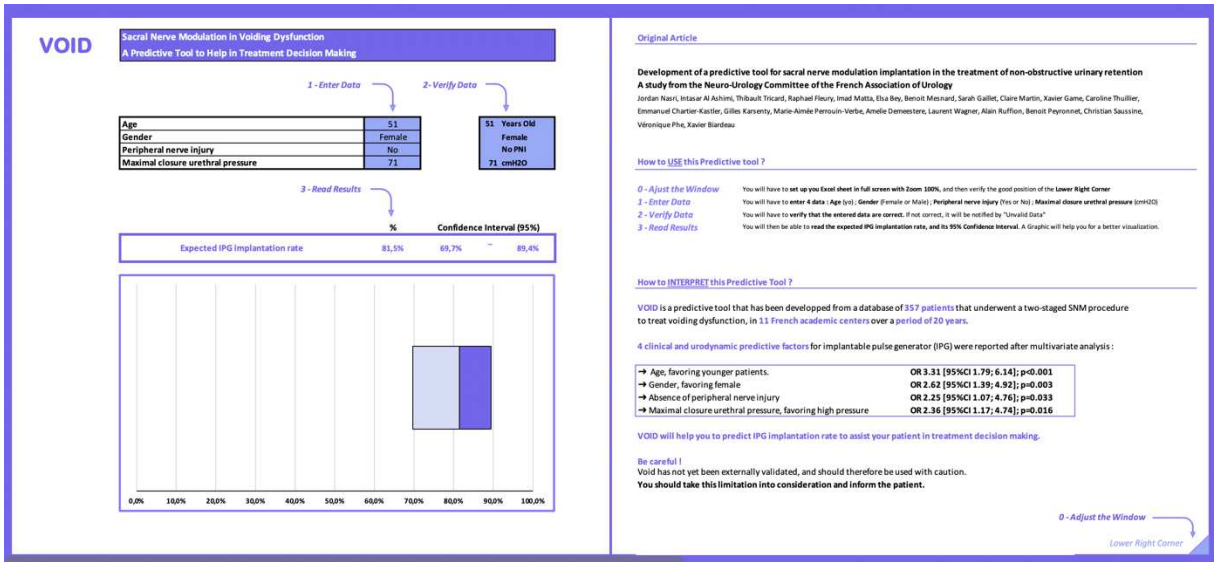
IPG: implantable pulse generator; **MUCP:** Maximal urethral closure pressure; **LMN:** Lower motor neuron

Supplementary Figure 2: internal validation using bootstrapping technique

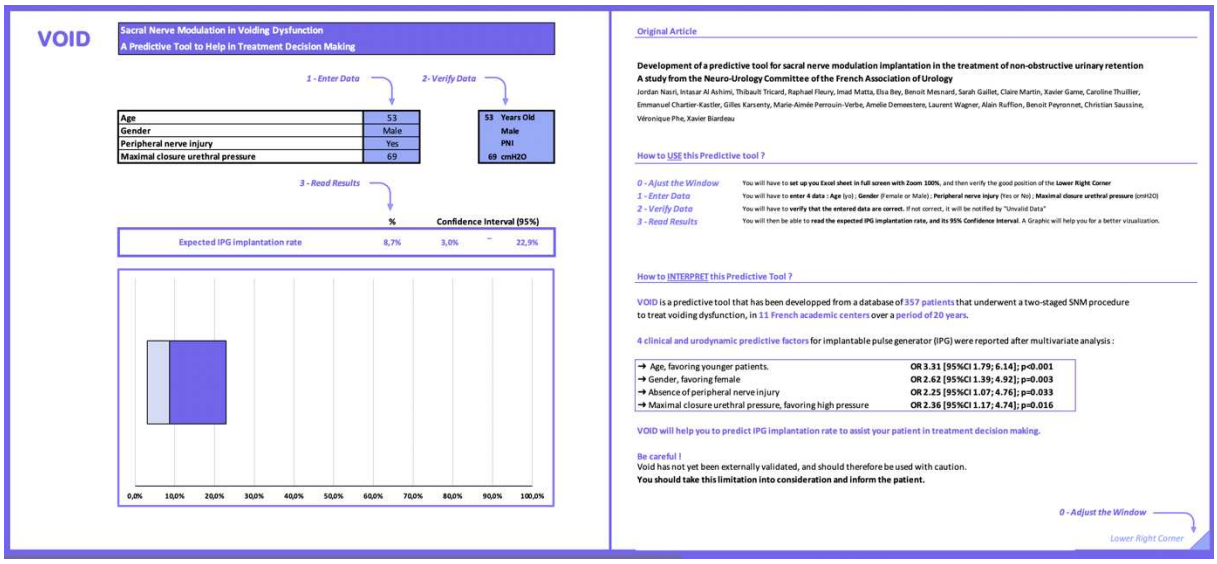


Supplementary Figure 3: Screenshots of the VOID Excel sheet

A. Screenshot corresponding to the most favorable combination of the 4 predictive factors, showing an expected IPG implantation rate of 81.5% [95%CI 67.9%-89.4%]



B. Screenshot corresponding to the most unfavorable combination of the 4 predictive factors, showing an expected IPG implantation rate of 8.7% [95%CI 3.0%-22.9%]



IPG: implantable pulse generator

PART II

AT THERAPY INITIATION,

QUESTIONING THE MECHANISMS OF ACTION

ACUTE AUTONOMIC NERVOUS SYSTEM RESPONSE TO DIRECT SACRAL NERVE ROOT STIMULATION IN LOWER URINARY TRACT DYSFUNCTION: A NEW APPROACH TO UNDERSTAND THE MECHANISM OF ACTION OF SACRAL NERVE MODULATION

In a fourth step, we questioned the effect of an acute sacral root stimulation on the balance of the ANS.

Indeed, the balance of the ANS seems to be modified or even altered in patients with lower urinary tract dysfunctions, particularly in the case of OAB/UUI or voiding dysfunction. However, the study of the mechanisms of action of the therapies proposed in these pathological contexts has rarely focused on understanding their effect on the balance of the ANS.

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ABSTRACT

Purpose: To assess acute autonomic nervous system (ANS) response to direct sacral nerve root (SNR) stimulation in the context of lower urinary tract dysfunction (LUTD).

Methods: In this retrospective monocentric study, patients undergoing two-stage SNM for overactive bladder (OAB), non-obstructive urinary retention (NOUR) or chronic bladder pain syndrome (CBPS) between March 2022 and June 2023 were analyzed. A standardized stimulation protocol was applied during the lead implantation, each of the four contact points being sequentially stimulated at the amplitude required to elicit anal motor response. Stimulations were labeled as StimA, StimB, StimC, and StimD, ordered by ascending order of minimum amplitude required for anal motor response. Heart rate variability (HRV) parameters were collected using PhysioDoloris Monitor, and computed through the time-domain (SDNN, RMSSD), the frequency-domain (LF, HF) and the graphical (ANI) methods.

Results: Fifty patients were analyzed, including 35 females. Twelve patients had an underlying neurological disease. Efficacy was deemed achieved in 16/28 patients (57.1%) with OAB and in 10/21 patients (47.6%) with NOUR. SDNN variability significantly increased during StimA to StimC, while maximum SDNN significantly increased only during StimA. ANI variability significantly increased during all four stimulations, while maximum ANI significantly increased only during StimA.

Conclusion: Direct stimulation of SNR is responsible for a significant increase in ANS and relative para-sympathetic nervous system activity, with a greater effect observed when the stimulation was delivered closer to the SNR. These results shed light on potential mechanisms underlying SNM, particularly regarding the treatment of ANS dysregulation in LUTD.

INTRODUCTION

Since its introduction in 1988 by Tanagho and Schmidt[1], sacral nerve modulation (SNM) has gained increasing recognition as a third-line therapy for overactive bladder (OAB)[2,3] as an alternative to clean intermittent self-catheterization (CISC) for managing non-obstructive urinary retention (NOUR)[4] and as a treatment option for chronic bladder pain syndrome (CBPS)[5] albeit to a lesser extent.

Despite demonstrating proven efficacy, with success rates ranging between 66.0%-85.0% for OAB treatment[6,7] and between 42.5%-100.0% for NOUR treatment[8], the precise mechanism of action of SNM remains not fully understood. Recent state-of-the-art reviews by De Wachter *et al.*[9] have emphasized that the only certainty regarding SNM's mechanisms of action lies in the role of afferences, which may play a key role in modulating spinal reflexes and brain centers. Interestingly, the role of the autonomic nervous system (ANS) in SNM's mechanisms of action, particularly in the context of lower urinary tract dysfunction (LUTD), has received limited consideration and lacks specific investigation. Nonetheless, it is important to remember that ANS - through the balance between the sympathetic (SNS) and the para-sympathetic (PSNS) nervous systems - plays a pivotal role in regulating the micturition cycle and is believed to contribute not only to OAB but also to certain types of NOUR[10,11]. To take this a step further, it is interesting to note that numerous studies have examined the relationship between ANS activity and OAB, utilizing cardiovascular autonomic testing[12], heart rate variability (HRV) analysis, skin sympathetic response[14], and even pupil reactivity[15]. Most of these studies reported significant changes in both SNS and PSNS activities in individuals with OAB compared to healthy volunteers. Similarly, Amarenco *et al.* assessed cardiovascular autonomic function in patients with NOUR related to Fowler's syndrome and reported an occult impairment of the ANS in this specific population[11]. Interestingly, it is precisely in this population of Fowler's syndrome that SNM seems to be most effective in managing NOUR[16].

Furthermore, in another area, SNM has been shown to have a substantial impact on ANS in rat models of acid-induced colitis. Specifically, Jiang *et al.*[17] and Tu *et al.*[18] found that both acute and chronic SNM reduced visceral hypersensitivity and displayed anti-inflammatory effects by enhancing vagal activity primarily through the spinal afferent-brain stem-vagal

efferent-colon pathway. SNM was accompanied by early and late modifications in autonomic function.

All these findings lead us to hypothesize that SNM's mechanisms of action on LUTD may, at least in part, be mediated through its influence on the ANS balance.

Therefore, the present exploratory study aims to assess the acute ANS response to SNM in the context of LUTD in human subjects.

METHODS

Study Design

The present work was designed as a retrospective monocentric study. All patients who had undergone a two-stage SNM to treat OAB, NOUR or CBPS between March 2022 and June 2023 were considered eligible. Clinical, urodynamic and SNM stimulation parameters at the time of lead implantation were retrieved from computerized medical records. Per-operative HRV was extracted from a monitoring system used in a daily practice in our operative room to monitor analgesia and was retrospectively computed.

Sacral nerve modulation implantation

Two systems, InterStim II™ and InterStim micro™ (Medtronic, Minneapolis, MN, USA), consisting of a neurostimulator and a quadripolar tined lead were used. All patients were implanted with a two-stage procedure under general anesthesia. During the first stage, the lead was implanted unilaterally according to the standardized lead placement technique described by Matzel *et al.*[19]. Lead correct position close to the sacral nerve root (SNR) was verified by the demonstration of a specific anal motor response (contraction of the anus) appearing during the stimulation carried out at the level of each of the 4 contact points (CP) numbered CP_0 , CP_1 , CP_2 and CP_3 . The lead was then connected to an external generator, which was followed by a 21-day test phase, during which improvement of symptoms was assessed. If the patient was significantly improved (50% or greater improvement in one or

more of its bothersome urinary parameters from baseline), an implantable pulse generator (IPG) was implanted during a second surgery.

Standardized sacral nerve root stimulation protocol

During the first stage, just after the lead has been released, a standardized stimulation protocol was conducted (Figure 1), with an electrical stimulation (rate = 14 Hz, pulse width = 210 µs) delivered at the minimum amplitude required to elicit anal motor response during 3 consecutive minutes. This stimulation was repeated on each of the four CPs, and a wash-out period (WOP), consisting in a pause of 2 minutes, was respected before and after each of these stimulations. Five time-analysis windows (TAW) were thus obtained, with TAW_B corresponding to the baseline. The stimulations successively applied at the level of the 4 CP, and corresponding to TAW_0 , TAW_1 , TAW_2 and TAW_3 were classified in ascending order according to the minimum amplitude required to obtain an anal motor response (StimA < StimB < StimC < StimD), with StimA being the stimulation of lowest intensity and thus corresponding to the CP positioned closest to the SNR.

Heart rate variability analysis

HRV analysis represents the study of the variations of the time intervals between 2 heartbeats (R-R intervals). Many spectral or time domain HRV analysis techniques have been described in the literature[20]. Frequency (or spectral) analysis consists of a time frequency transformation (Fast Fourier transform or Wavelet transform), which allow to distinguish 3 frequency areas: very low frequencies - from 0 to 0.04 Hz - reflecting thermoregulation and endocrine activity, low frequencies (LF) - from 0.04 to 0.15 Hz - reflecting both SNS and PSNS activities associated with the baroreflex, and high frequencies (HF) - from 0.15 to 0.4 Hz - representative of absolute PSNS activity. Time domain analysis includes the standard deviation of normal-to-normal R-R intervals (SDNN), which represents the overall variability of the R-R series; and root mean square of successive differences between adjacent R-R intervals (RMSSD) which represents the short-term variability which is linked to the PSNS.

R-R series were recorded using a unique monitoring system used in daily clinical practice for analgesia monitoring, ANI Monitor V1 (Mdoloris Medical Systems, Loos, France). This monitor

uses a graphical computation method allowing to obtain the Analgesia Nociception Index (ANI) which reflects the relative variability of the PSNS[21]. The ANI monitor also allows to export raw R-R intervals with a precision of ± 4 ms, within a 2-minute TAW. R-R series exported from the ANI monitor were post-analyzed to compute time-domain markers, including SDNN and RMSSD, and frequency-domain markers including LF and HF (Supplementary Table 1). Minimum, maximum and variability (maximum - minimum) values of each of these variables were evaluated during TAW $_B$ as well as during TAW_0 to TAW_3 .

Outcomes of interest

The primary endpoint was the comparison of SDNN between baseline and during the stimulations StimA to StimD. The secondary endpoints included the comparison of RMSSD, LF, HF and ANI between baseline and during the stimulations StimA to StimD.

Statistical analysis

Descriptive variables were expressed as median (1^{st} - 3^{rd} quartile). For comparison, the normality of distribution was assessed using the Shapiro-Wilk test. Quantitative variables were expressed as mean (± standard deviation) when normally distributed and as median (1^{st} - 3^{rd} quartile) when not normally distributed. To assess the differences between the baseline and StimA, StimB, StimC and StimD, a T test (for normal distribution) or Wilcoxon test were carried out with a Bonferroni correction for multiple comparisons. Statistical significance was assumed for $p<0.05$. A Friedman or an ANOVA test could not be performed as there was not the same number of stimulations per patient.

RESULTS

Patients' characteristics at baseline

Out of the 53 patients who underwent a two-stage SNM procedure, 3 patients were excluded from the analysis due to artifacts measurement, and HRV could be computed for 50 patients - including 28 with OAB, 21 with NOUR and 1 with CBPS. Patients' characteristics at baseline

are detailed in Table 1. Stimulations could be delivered on all four CPs for 32 patients, while it could only be delivered on three, two and only one of the four CPs for 11, 6 and 1 patients, respectively - due to the absence of anal motor response. Data related to lead implantation and standardized stimulations are detailed in Table 2, while distribution of CPs in the constitution of StimA to StimD groups are presented in Supplementary Figure 1. Efficacy was deemed achieved in 16/28 patients (57.1%) with OAB (Supplementary Table 2) and in 10/21 patients (47.6%) with NOUR (Supplementary Table 3).

Outcomes of interest

Primary outcome

SDNN variability significantly increased during StimA to StimC, going from 6.92 at baseline to 9.52, 9.40 and 8.72, respectively. Maximum SDNN significantly increased during StimA, going from 16.36 at baseline to 19.39 (Table 3).

Secondary outcomes

RMSSD variability significantly increased during StimB and StimC, going from 4.06 at baseline to 5.61 and 8.22, respectively. During StimC, it was accompanied with a significant decrease in minimum RMSSD, going from 9.38 at baseline to 8.36.

ANI variability significantly increased during all the four stimulations, going from 17.87 at baseline to 29.01, 25.91, 28.48 and 26.76 during StimA to StimD, respectively. In parallel, minimum ANI significantly decreased during StimA, StimC and StimD going from 69.47 at baseline to 62.39, 62.59, and 64.09, respectively. Maximum ANI significantly increased during StimA, going from 90.40 at baseline to 96.83.

DISCUSSION

Here, we reported the first assessment of the ANS acute response to a direct unilateral SNR stimulation. As the primary endpoint, we compared SDNN at baseline and during stimulations applied from the four CPs of the quadripolar lead. The significant increase in SDNN variability

during StimA to StimC suggests a significant modification in overall ANS activity. It is noteworthy that as the amplitude of the stimulation to elicit anal motor response decreased, the variability in SDNN increased and became more significant, suggesting that the overall activity of the ANS was increased to a greater extent when the stimulation was performed closer to the SNR. We have also demonstrated that StimA was the only one capable to significantly increase the maximum SDNN. Among secondary endpoints, ANI seemed to be the most interesting, since its variability significantly increased during the four stimulations applied when compared to baseline, with a higher ANI variability reported with stimulations of lower amplitude, suggesting a higher variation of the relative PSNS activity when the stimulation was performed closer to the SNR. We also demonstrated that StimA was the only one capable to significantly increase the maximum ANI.

It is important to highlight that the changes in the ANS activity that we have reported here should not be attributed to painful stimulation, as evidenced by the values of the ANI - an index originally developed to monitor intraoperative imbalance between analgesia and nociception. In fact, ANI, never decreased under 50 - the threshold below which analgesic control is considered inadequate - all along the baseline and the four stimulations. A significant increase in maximum ANI was even observed during StimA.

Taken all together, these findings suggest that acute stimulation of the SNR has the potential to significantly influence ANS activity. This is demonstrated by a notable rise in overall ANS activity, as evidenced by a significant increase in maximum SDNN at the CP located closest to the SNR. This increase is further correlated with heightened relative PSNS variability, evidenced by a significant increase in maximum ANI at the CP located closest to the SNR. Although we acknowledge the controlled experimental nature of this study, limited to the evaluation of the acute response of the ANS to direct stimulation of SNR under general anesthesia, and therefore the impossibility of drawing any definitive conclusions regarding the mid- to long-term impact of such stimulation on ANS activity- particularly during bladder filling or emptying- it is reasonable to hypothesize that SNM's mechanisms of action may involve, at least in part, an increase in PSNS activity.

To better understand the significance and the importance of our findings, it is important to note that they directly resonate with previous reports regarding ANS abnormalities within the context of LUTD, and more precisely in the context of OAB. Even if results have long been contradictory[22], recent research presented by Chen *et al.*[14] concerning the investigation of skin sympathetic response in OAB patients, along with the studies conducted by Choi *et al.*[23] and Kim *et al.*[24] examining HRV in OAB patients, provide insights into abnormally heightened SNS activity among individuals with OAB. Notably, these three studies demonstrated an increase in average skin sympathetic nerve activity[14] and a decrease in SDNN[23] associated with an elevation in the LF/HF ratio[24] - indicative of a relative state of SNS hyperactivity over PSNS activity - in OAB patients when compared to healthy volunteers or patients with stress urinary incontinence. Thus, and in view of what we have been able to report in the present article, it is possible that SNM could potentially improve OAB, and maybe other LUTD, by rebalancing the ANS notably by increasing PSNS activity and counteracting the SNS hyperactivity. Beyond these preliminary results, the value of the present study probably lies above all in demonstrating an incremental advance in the study of neuro-pathophysiology of LUTD, by taking advantage of an existing human model of nerve stimulation.

It must be acknowledged that this is a retrospective study encompassing a relatively heterogeneous population, both neurologic and non-neurologic, undergoing a two-stage SNM for various LUTDs, including OAB, NOUR, and to a lesser extent CBPS. Among OAB patients, we reported a lower implantation rate than previously reported in the literature[6,7]. However, as this group included only 28 patients - which limits interpretation - and as this was not the aim of our study, we decided not to focus on. However, it is important to note the significant variation in respiratory rate between patients. Even though the ANI has been developed in such a way that it is not at all sensitive to variations in respiratory rate[25], it is possible that the HFs have been impacted by these variations.

While we have standardized the patient clinical pathway, significant variations undoubtedly persist, particularly concerning anesthesia protocols that differed between patients and could have potentially impacted the outcomes. It is also crucial to recall that, in the absence of a prior similar study, we developed a standardized stimulation protocol that took into consideration both the inertia of the ANS and the time constraints of the operating room. In addition, we decided to set the stimulation amplitude at the level of the motor response,

which, although not physiological, was considered the only reproducible stimulation under general anesthesia. It is likely that this protocol can be further refined for optimization. However, based on the time frame for ANS modification - under 25 seconds as supposed by the definitions of the HRV parameters[20] - and the 2-minute TAW used by the ANI monitor, we believe that our protocol was able to capture the modifications of the ANS occurring in response to the stimulation of the SNR.

We advocate for future research protocols to confirm our preliminary results, but also to assess whether the ANS response to direct SNR stimulation correlates with clinical and/or urodynamic efficacy of SNM. Although we opted for HRV because of the widespread use of the ANI monitor in our routine operative room practice. It would be interesting to consider the use of other ANS analysis tools, including cutaneous sympathetic response or pupil reactivity in combination with HRV, to further investigate absolute SNS activity in this context.

CONCLUSION

The present exploratory work provides a glimpse of the involvement of the ANS in the SNM's mechanism of action and will probably open new avenues for reflection.

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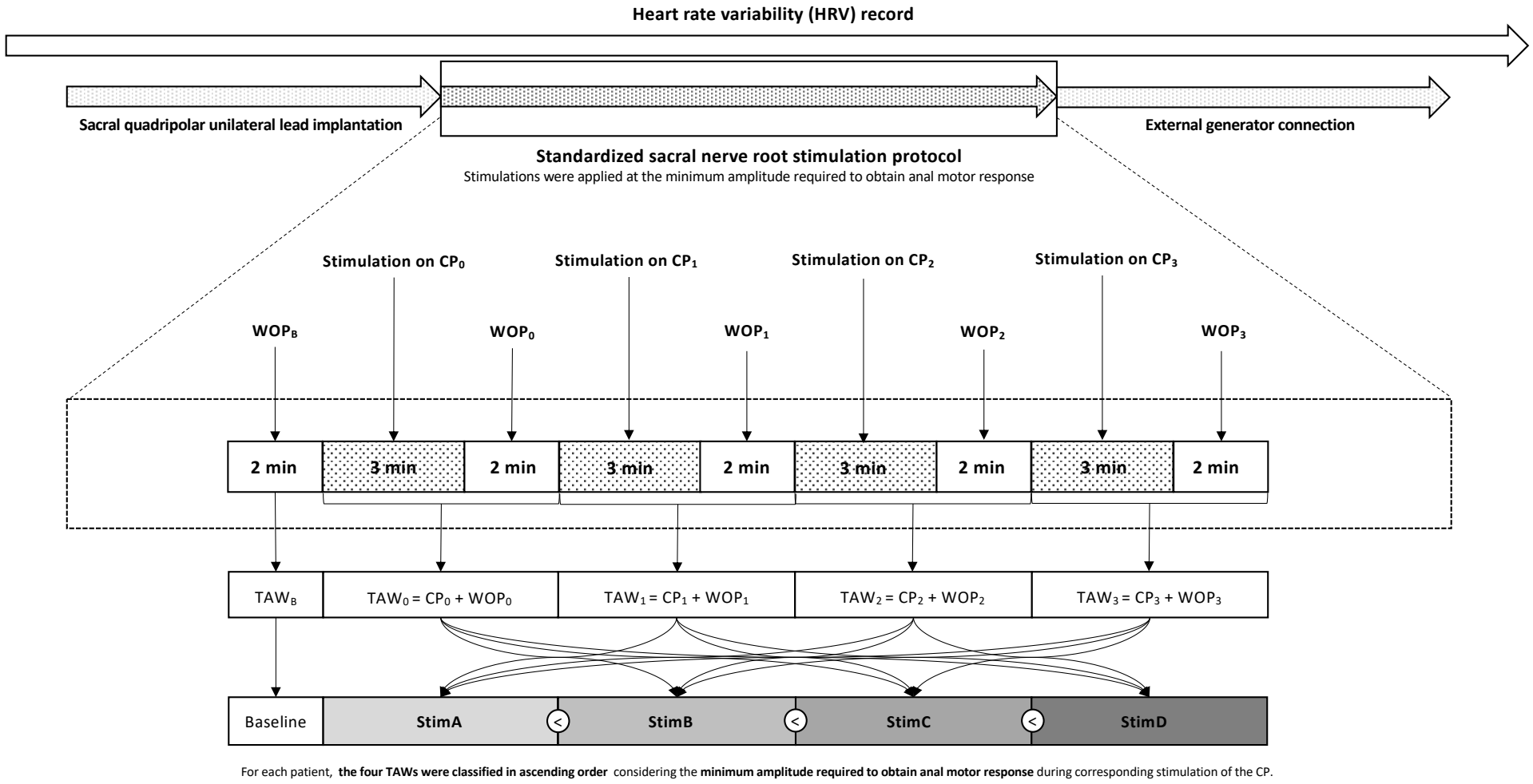
Figure 1: Standardized sacral nerve root stimulation protocol



CP: Contact point; **WOP:** Wash-out period; **TAW:** Time analysis window

Table 1: Patients' characteristics at baseline

	Overall N = 50		OAB N = 28		NOUR N = 21	
Gender (male)	15	30.0%	8	28.6%	7	33.3%
Age (years) *median (Q1-Q3)*	51.0	(39.3 - 62.0)	61.5	(46.5 - 66.5)	43.0	(38-41.5)
BMI (kg/m² *) median (Q1-Q3)*	24.2	(21.1 - 30.9)	25.8	(22.5 - 32.95)	22.8	(19-22.8)
Underlying neurological disease	**12**	**24.0%**	**11**	**39.3%**	**1**	**4.8%**
Multiple sclerosis	4[1]	8.0%	4[1]	14.3%	0	0.0%
Incomplete spinal cord injury	1[2]	2.0%	1[2]	3.6%	0	0.0%
Brain injury	3[3]	6.0%	3[3]	10.7%	0	0.0%
Parkinson disease	2[4]	4.0%	2[4]	7.1%	0	0.0%
Cerebral palsy	2	4.0%	1	3.6%	1	4.8%
Deep pelvic endometriosis	**9**	**25.7%**	**2**	**10.0%**	**7**	**50.0%**
History of SUI surgery	**7**	**14.0%**	**5**	**17.9%**	**2**	**9.5%**
Sub-urethral sling	7	14.0%	5	17.9%	2	9.5%
Bulking agent	2	4.0%	1	3.6%	1	4.8%
ACT/pro-ACT balloons	2	4.0%	2	7.1%	0	0.0%
Artificial urinary sphincter	2	4.0%	2	7.1%	0	0.0%
Colposuspension	2	4.0%	2	7.1%	0	0.0%
History of vaginal prolapse surgery*	**3**	**8.6%**	**3**	**15.0%**	**0**	**0.0%**
Anterior *	1	2.9%	1	5.0%	0	0.0%
Posterior*	1	2.9%	1	5.0%	0	0.0%
Anterior + Posterior*	1	2.9%	1	5.0%	0	0.0%
Sacrocolpopexy*	1	2.9%	1	5.0%	0	0.0%
Vaginal repair*	2	5.7%	2	10.0%	0	0.0%
History of ECD surgery*	**8**	**16.0%**	**2**	**10.0%**	**6**	**42.9%**
History of Prostate surgery**	**6**	**40.0%**	**3**	**37.5%**	**3**	**42.8%**
Radical prostatectomy**	2	13.3%	1	12.5%	1	14.3%
Endoscopic resection/enuclation of the prostate**	4	26.7%	2	25.0%	2	28.6%
History of LUTS therapies						
Alpha-blocker	15	30.0%	5	17.9%	10	47.6%
Antimuscarinic	27	54.0%	24	85.4%	3	14.3%
Beta-3 adrenergic	7	14.0%	7	25.0%	0	0.0%
Intra-vesical botulinum toxin a	7	14.0%	6	21.4%	1	4.8%
onabotulinum toxin a (50 U)	3	6.0%	3	10.7%	0	0.0%
onabotulinum toxin a (100 U)	3	6.0%	3	10.7%	0	0.0%
onabotulinum toxin a (200 U)	3	6.0%	2	7.1%	1	4.8%
onabotulinum toxin a (300 U)	2	4.0%	2	7.1%	0	0.0%
abobotulinum toxin a	1	2.0%	1	3.6%	0	0.0%
Transcutaneous tibial nerve stimulation	17	34.0%	12	42.9%	5	23.8%
Concurrent LUTS therapies						
Alpha-blocker	3	6.0%	1	3.6%	2	9.5%
Antimuscarinic	2	4.0%	2	7.1%	0	0.0%
Beta-3 adrenergic	2	4.0%	2	7.1%	0	0.0%

Values are presented as frequency (percentage), unless otherwise indicated. * Considering only female population; ** Considering only male population
OAB: Overactive bladder; **NOUR:** Non-obstructive urinary retention; **BMI:** Body mass index; **SUI:** Stress urinary incontinence; **DPE:** Deep pelvic **endometriosis**

1: 4 patients presenting with a relapsing-remitting multiple sclerosis with a median EDSS = 3.5 (3 - 4) and a median duration of the disease of 20.5 years (14 - 29.5)
2: 1 patient presenting with an incomplete (AIS E) C3 spinal cord injury
3: 3 patients presenting with a history of ischemic stroke, with a median duration of the brain injury of 5 years (5 - 6)
4: 2 patients presenting with an idiopathic Parkinson disease, with a median duration of the disease of 6 years (4.5 - 7)

Table 2: Data related to sacral quadripolar lead implantation and standardized stimulation

	Overall N = 50		OAB N = 28		NOUR N = 21	
SNM device						
Interstim II	26	52.0%	18	64.3%	7	33.3%
Interstim Micro	24	48.0%	10	35.7%	14	66.6%
Lead implantation						
Sacral S3 root	47	94.0%	35	89.3%	21	100.0%
Sacral S4 root	3	6.0%	3	10.7%	0	0.0%
Right side	29	58.0%	15	53.6%	13	61.9%
Amplitude to obtain an anal motor response (mA)						
CP_0 *median (Q1-Q3)*	1.6	(1.0 - 2.9)	1.6	(1.2 - 3.0)	1.7	(1.0 - 2.3)
CP_1 *median (Q1-Q3)*	1.4	(1.0 - 2.3)	1.2	(1.0 - 1.8)	1.9	(1.1 - 3.4)
CP_2 *median (Q1-Q3)*	1.0	(0.6 - 1.7)	0.8	(0.5 - 1.5)	1.2	(0.9 - 2.0)
CP_3 *median (Q1-Q3)*	1.5	(0.9 - 2.5)	1.6	(1.1 - 2.5)	1.3	(0.6 - 2.2)
StimA *median (Q1-Q3)*	0.7	(0.5 - 1.0)	0.6	(0.4 - 0.9)	0.9	(0.6 - 1.1)
StimB *median (Q1-Q3)*	1.2	(0.9 - 1.7)	1.2	(0.8 - 1.6)	1.3	(1.0 - 1.9)
StimC *median (Q1-Q3)*	2.2	(1.4 - 2.7)	1.9	(1.4 - 2.6)	2.3	(1.7 - 3.2)
StimD *median (Q1-Q3)*	2.3	(1.6 - 2.9)	2.4	(1.6 - 3.0)	2.3	(1.7 - 3.3)
Type of Anesthetics						
Halogenated inhalational anesthetics	**43**	**(86.0%)**	**24**	**85.7%**	**18**	**85.7%**
Desflurane	22	44.0%	9	32.1%	12	57.1%
[Desflurane] (MAC) *median (Q1-Q3)*	5.3	(4.5-6.0)	5.1	(4.6 - 5.4)	5.45	(4.5-7.0)
Sevoflurane	21	42.0%	15	53.6%	6	28.6%
[Sevoflurane] (MAC) *median (Q1-Q3)*	1.8	(1.4-2.0)	1.8	(1.4-1.9)	2.05	(2.0-2.2)
Intravenous anesthetics	**7**	**14.0%**	**4**	**14.3%**	**3**	**14.2%**
Propofol	7	14.0%	4	14.3%	3	14.2%
[Propofol] (ng/ml) *median (Q1-Q3)*	3.3	(2.3-3.5)	3.5	(3.38-3.5)	2	(2.0-3.5)
Type of Analgesics						
Remifentanil	36	72.0%	19	67.9%	16	76.2%
[Remifentanil] (ng) *median (Q1-Q3)*	2.5	(2.5-3.0)	2.5	(2.25 - 3.0)	3.0	(2.5-3.1)
Sufentanil	14	28.0%	9	32.1%	5	23.8%
[Sufentanil] (µg) *median (Q1-Q3)*	18.8	(15.0-20.0)	20.0	(15.0 - 20.0)	15.0	(15.0-20.0)
Respiratory rate (per min)	**14.0**	**(14.0 - 16.0)**	**14.0**	**(12.5 - 16.0)**	**14.0**	**(14.0 - 16.0)**

Values are presented as frequency (percentage), unless otherwise indicated.
OAB: Overactive bladder; **NOUR:** Non-obstructive urinary retention; **SNM:** Sacral nerve modulation; **CP:** Contact point; **MAC:** Minimum alveolar concentration

Stim A, StimB, StimC, StimD correspond to the four stimulations successively delivered on the four contact points (CP_0 to CP_3) during the four time-analysis windows (TAW 0 to TAW3) and classified in ascending order according to the minimum amplitude required to elicit anal motor response (StimA < StimB < StimC < StimD) - with StimA being the stimulation of lowest intensity and thus corresponding to the CP positioned closest to the SNR.

Table 3: Heart rate variability analysis

		Baseline N=50		StimA N=50		p-value*	StimB N=49		p-value*	StimC N=43		p-value*	StimD N=32		p-value*
SDNN															
	Delta	6.92	(3.77 - 10.60)	9.52	(6.24 - 14.83)	<0.001	9.40	(6.16 - 14.11)	<0.001	8.72	(5.80 - 16.83)	0.02	8.97	(5.87 - 13.19)	0.094
	Min	8.43	(5.21 - 14.72)	8.61	(5.64 - 12.68)	1	8.94	(5.58 - 11.27)	0.654	7.97	(4.38 - 12.91)	0.292	8.43	(5.67 - 12.25)	1
	Max	16.36	(11.31 - 21.46)	19.39	(14.97 - 29.21)	0.002	18.74	(13.82 - 26.97)	0.285	17.31	(13.30 - 28.46)	0.116	20.06	(13.99 - 25.40)	0.369
RMSSD															
	Delta	4.06	(2.21 - 9.49)	5.22	(3.16 - 10.98)	0.065	5.61	(3.82 - 15.67)	<0.001	8.22	(4.01 - 18.57)	< 0.001	4.69	(2.86 - 11.72)	0.669
	Min	9.38	(4.97 - 13.28)	9.79	(5.12 -12.51)	0.417	9.09	(5.59 - 14.28)	0.639	8.36	(4.42 - 13.25)	0.03	9.08	(4.73 - 13.14)	0.586
	Max	16.13	(8.2 - 25.37)	15.34	(9.29 - 24.42)	1	16.62	(11.15 - 27.50)	0.684	19.63	(11.73 - 32.00)	0.116	14.88	(9.95 - 27.02)	1
LF															
	Delta	0.03	(0.008 - 0.08)	0.03	(0.01 - 0.09)	0.216	0.03	(0.02 - 0.14)	0.243	0.05	(0.02 - 0.18)	0.016	0.04	(0.01 - 0.12)	0.351
	Min	0.04	(0.01 - 0.08)	0.04	(0.01 - 0.07)	0.074	0.03	(0.01 - 0.08)	0.7	0.03	(0.01 - 0.07)	1	0.03	(0.01 - 0.07)	1
	Max	0.09	(0.03 - 0.19)	0.07	(0.03 - 0.18)	0.93	0.08	(0.03 - 0.22)	1	0.09	(0.04 -0.27)	0.116	0.09	(0.03 -0.26)	1
HF															
	Delta	0.005	(0.002 - 0.02)	0.009	(0.004 - 0.023)	0.029	0.009	(0.005 - 0.04)	0.041	0.014	(0.005 - 0.05)	0.007	0.007	(0.004 - 0.04)	1
	Min	0.01	(0.004 - 0.03)	0.01	(0.003 - 0.02)	0.002	0.01	(0.004 - 0.02)	0.105	0.01	(0.003 - 0.02)	0.599	0.008	(0.003 - 0.02)	0.038
	Max	0.02	(0.006 - 0.05)	0.02	(0.008 - 0.05)	1	0.02	(0.01 - 0.07)	0.531	0.03	(0.01 - 0.09)	0.116	0.02	(0.01 - 0.1)	1
ANI															
	Delta	17.87	±11.32	29.01	±14.82	<0.001	25.91	±15.29	0.002	28.48	±15.91	<0.001	26.76	±19.21	0.004
	Min	69.47	±19.37	62.39	±20.00	0.038	63.92	±21.65	0.054	62.59	±21.72	0.03	64.09	±26.01	0.029
	Max	90.40	(83.15 - 98.65)	96.83	(85.98 -99.90)	0.044	96.39	(83.55 - 99.85)	1	97.34	(87.85 - 99.69)	0.17	94.46	(83.80 -100)	1

Values are presented as median (Q1-Q3), or as mean (*±SD*)

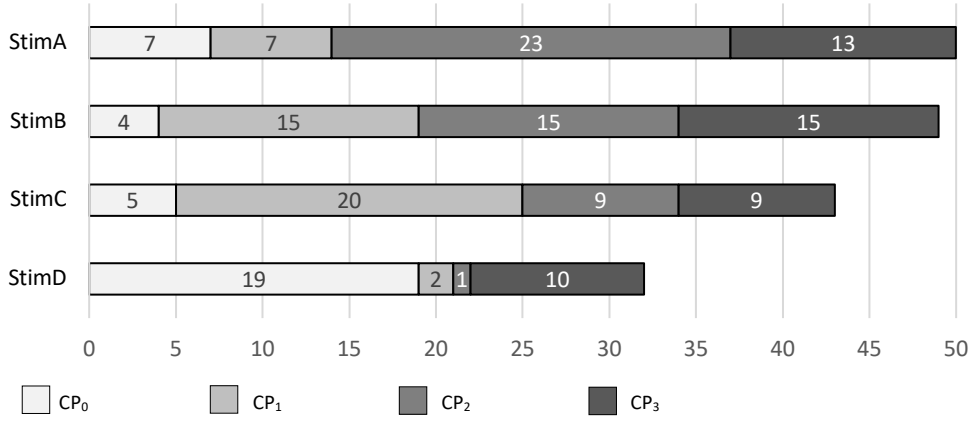
*: when compared with baseline

SDNN: standard deviation of NN intervals; **RMSSD:** root mean square of successive differences; **LF:** low frequency; **HF:** High frequency; **ANI:** Analgesia Nociception Index

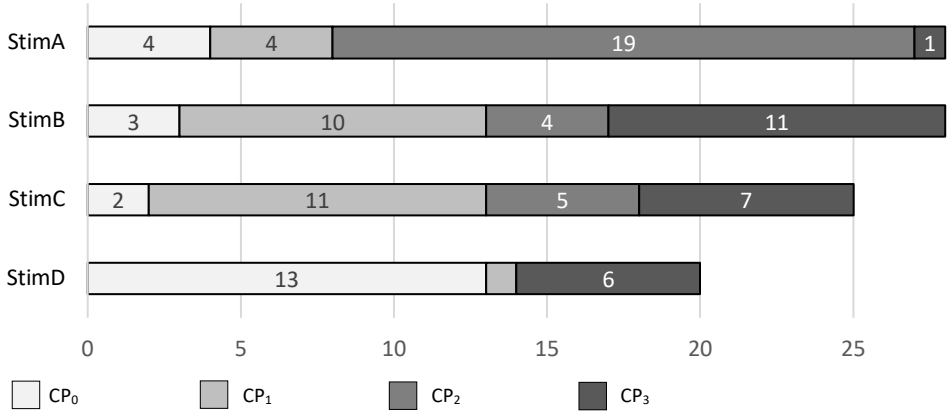
Stim A, StimB, StimC, StimD correspond to the four stimulation successively delivered on the four contact points (CP_0 to CP_3) during the four time-analysis windows (TAW 0 to TAW3) and classified in ascending order according to the minimum amplitude required to obtain an anal motor response (StimA < StimB < StimC < StimD) - with StimA being the stimulation of lowest intensity and thus corresponding to the CP positioned closest to the nerve.

Supplementary Figure 1: Distribution of contact points in the constitution of StimA to StimD groups

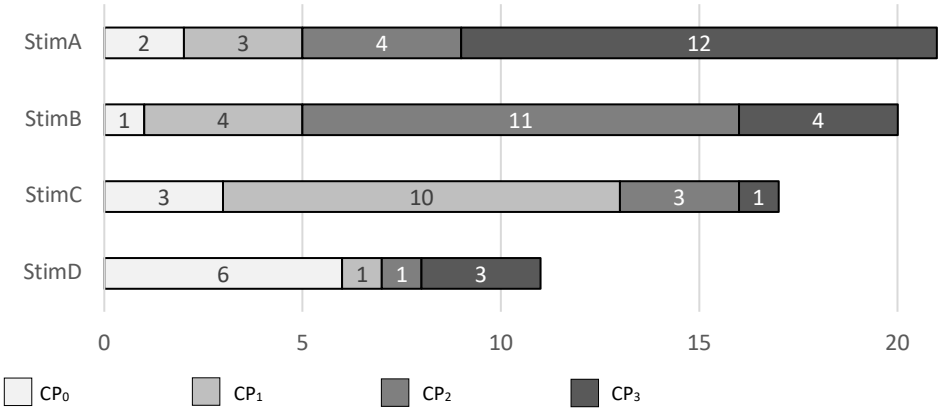
A. Overall Population (N = 50)



B. OAB Population (N = 28)



C. NOUR Population (N = 21)



CP: Contact Point; **OAB:** Overactive bladder; **NOUR:** Non-obstructive urinary retention

Stim A, StimB, StimC, StimD correspond to the four stimulations successively delivered on the four contact points (CP_0 to CP_3) during the four time-analysis windows (TAW 0 to TAW3) and classified in ascending order according to the minimum amplitude required to elicit anal motor response (StimA < StimB < StimC < StimD) - with StimA being the stimulation of lowest intensity and thus corresponding to the CP positioned closest to the SNR.

Supplementary Table 1: Heart rate variability computation and interpretation

Variable HRV	Computation	Interpretation
Time-domain analysis		
RMSSD	The root mean square of successive differences (RMSSD) between successive RR intervals was computed over 100 RR intervals, which correspond to approximately 2 minutes.	High frequency variability of the ANS, mainly of PSNS origin
SDNN	The standard deviation of normal to normal (SDNN) RR intervals was computed over 100 RR intervals, which correspond to approximately 2 minutes.	. Overall variability of the ANS
Spectral analysis		
LF	Low frequency (LF) was based on spectral analysis of the RR series. LF was computed between 0.04 - 0.15 Hz using a wavelet transform (e.g. Daubechies 4-wavelet) performed on a 64-second window resampled at 8 Hz. LF was then average over 56 seconds given window of 2 minutes duration.	Activity of both the SNS and the PSNS
HF	High frequency (HF) was based on spectral analysis of the RR series. HF was computed in the same way as LF but between 0.15 -0.4 Hz. HF was then average over 56 seconds given window of 2 minutes duration.	Absolute variability of the PSNS
Graphical analysis		
ANI	The ANI is a graphical index of the magnitude of HF oscillations. The RR series were resampled at 8 Hz, centred, and normalized in 64-second windows. The signal was band-pass filtered a wavelet transform to retain HF content only. ANI correspond to the magnitude of these oscillations and was measured as the surface area between the upper and lower envelopes. ANI was then average over 56 seconds given window of 2 minutes duration.	Relative variability of the PSNS

SDNN: standard deviation of NN intervals; **RMSSD:** root mean square of successive differences; **LF:** low frequency; **HF:** High frequency; **ANI:** Analgesia Nociception Index

ANS: autonomic nervous system; **SNS:** sympathetic nervous system; **PSNS:** para-sympathetic nervous system

Supplementary Table 2: Evolution of lower urinary tract symptoms and urodynamic parameters in OAB patients

Overall OAB population (N= 28)	**Before SNM test phase**		**At the end of SNM test phase**	
Voiding mode				
Spontaneous voiding	26	92.8%	27	96.4%
Spontaneous voiding + CISC	1	3.6%	0	0.0%
CISC	1	3.6%	1	3.6%
3-day bladder diary				
Frequency	10.0	(8.0 - 11.3)	7.5	(6.0 - 10.0)
Nocturia	2.0	(1.0 - 3.0)	1.0	(0.0 - 2.3)
Number of urgency episodes / 24h	10.0	(5.0 - 11.0)	0.5	(0.0 - 5.3)
Number of UUI episodes / 24h	3.5	(0.0 - 5.0)	0.0	(0.0 - 2.3)
Multichannel urodynamic study				
Volume at first bladder sensation (mL)	128.0	(71.0 - 172.0)	151.5	(96.8 - 208.3)
Maximum cystometric capacity (mL)	170.0	(131.0 - 258.0)	189.0	(134.5 - 338.0)
Detrusor overactivity	18	64.3%	12	42.9%

OAB population that underwent IPG implantation (N= 16)	**Before SNM test phase**		**At the end of SNM test phase**	
Voiding mode				
Spontaneous voiding	16	100.0%	16	100.0%
3-day bladder diary				
Frequency	10.0	(8.8 - 12.3)	7.0	(5.8 - 8.3)
Nocturia	3.0	(1.0 - 3.0)	0.5	(0.0 - 1.3)
Number of urgency episodes / 24h	9.0	(5.0 - 10.0)	0.0	(0.0 - 1.0)
Number of UUI episodes / 24h	5.0	(0.0 - 5.0)	0.0	(0.0 - 0.5)
Multichannel urodynamic study				
Volume at first bladder sensation (mL)	128.0	(60.0 - 147.0)	169.0	(121.0 - 212.0)
Maximum cystometric capacity (mL)	194.0	(144.5 - 257.5)	282.5	(168.8 - 354.3)
Detrusor overactivity	11	68.8%	6	37.5%

OAB population that underwent lead explantation (N= 12)	**Before SNM test phase**		**At the end of SNM test phase**	
Voiding mode				
Spontaneous voiding	10	83.4%	11	91.7%
Spontaneous voiding + CISC	1	8.3%	0	0.0%
CISC	1	8.3%	1	8.3%
3-day bladder diary				
Frequency	9.5	(8.0 - 10.3)	8.5	(7.8 - 10.0)
Nocturia	2.0	(1.0 - 3.0)	2.0	(1.0 - 3.0)
Number of urgency episodes / 24h	10.0	(2.8 - 12.0)	6.5	(1.5 - 10.0)
Number of UUI episodes / 24h	1.0	(0.0 - 4.3)	0.5	(0.0 - 3.3)
Multichannel urodynamic study				
Volume at first bladder sensation (mL)	122.5	(71.8 - 181.5)	110.5	(78.5 - 171.8)
Maximum cystometric capacity (mL) *median (IQR)*	158.0	(126.0 - 271.8)	135.0	(122 - 326.0)
Detrusor overactivity	7	58.3%	6	50.0%

Values are presented as frequency (percentage), or as median (Q1-Q3).

OAB: Overactive bladder; **SNM:** Sacral nerve modulation; **CISC:** Clean intermittent self-catheterization; **IPG:** Implantable pulse generator

Supplementary Table 3: Evolution of lower urinary tract symptoms and urodynamic parameters in NOUR patients

Overall NOUR population (N= 21)	**Before SNM test phase**		**At the end of SNM test phase**	
Voiding mode				
Spontaneous voiding	4	19.0%	11	52.3%
Spontaneous voiding + CISC	5	23.8%	4	19.0%
CISC	9	42.9	4	19.0%
Third-person catheterization	1	4.8%	0	0.0%
Supra-pubic catheter	2	9.5%	2	9.5%
3-day bladder diary *				
Frequency	6.0	(6.0 - 8.0)	6.0	(5.5 - 7.5)
Nocturia	0.0	(0.0 - 0.0)	0.0	(0.0 - 0.0)
Multichannel urodynamic study*				
Voided volume (mL)	75.0	(65.0 -211.0)	245.5	(142.5 - 303.8)
Q_{max} (mL)	9.5	(6.9 -14.9)	10.2	(8.4 - 15.3)
Post-void residual volume (mL)	293.0	(100.8 - 422.3)	168.0	(15.0 - 223.5)
Bladder voiding efficiency ratio (%)	19.9%	(12.5% - 66.7%)	44.2%	(26.8% - 66.3%)
Volume at first bladder sensation (mL)	253.5	(187.8 - 334.3)	198.0	(139.0 - 229.0)
Maximum cystometric capacity (mL)	393.5	(317.5 - 512.8)	388.0	(318.5 - 529.0)

NOUR population that underwent IPG implantation (N=10)	**Before SNM test phase**		**At the end of SNM test phase**	
Voiding mode				
Spontaneous voiding	3	30.0%	9	90.0%
Spontaneous voiding + CISC	3	30.0%	1	10.0%
CISC	4	40.0%	0	0.0%
Third-person catheterization	0	0.0%	0	0.0%
Supra-pubic catheter	0	0.0%	0	0.0%
3-day bladder diary *				
Frequency	6.0	(6.0 - 8.0)	6.5	(5.3 - 8.0)
Nocturia	0.0	(0.0 - 0.0)	0.0	(0.0 - 0.0)
Multichannel urodynamic study *				
Voided volume (mL)	90.0	(65.0 - 317.0)	316.0	(255.5 - 347.5)
Q_{max} (mL)	11.2	(8.7 - 13.8)	15.1	(11.0 - 16.4)
Post-void residual volume (mL)	297.0	(30.0 - 422.3)	15.0	(0.0 - 83.0)
Bladder voiding efficiency ratio (%)	32.4%	(9.9% - 91.7%)	81.6%	(61.2% - 92.0%)
Volume at first bladder sensation (mL)	238.0	(173.3 - 300.5)	170.0	(141.0 - 203.5)
Maximum cystometric capacity (mL)	393.5	(357.8 - 425.0)	320.0	(309.5 - 368.0)

NOUR population that underwent lead explantation (N=11)	**Before SNM test phase**		**At the end of SNM test phase**	
Voiding mode				
Spontaneous voiding	1	9.1%	2	18.2%
Spontaneous voiding + CISC	2	18.2%	3	27.2%
CISC	5	45.4%	4	36.4%
Third-person catheterization	1	9.1%	0	0.0%
Supra-pubic catheter	2	18.2%	2	18.2%
3-day bladder diary *				
Frequency	6.0	(6.0 - 8.0)	6.0	(6.0 - 6.0)
Nocturia	0.0	(0.0 - 0.0)	0.0	(0.0 - 0.0)
Multichannel urodynamic study*				
Voided volume (mL)	71.5	(65.8 - 111.0)	174.0	(51.5 - 245.5)
Q_{max} (mL)	8.0	(6.2 - 12.2)	9.9	(6.9 - 10.2)
Post-void residual volume (mL)	285.0	(204.3 - 350.0)	200.0	(172.0 - 458.5)
Bladder voiding efficiency ratio (%)	17.6%	(12.5% - 30.8%)	28.6%	(15.7% - 44.2%)
Volume at first bladder sensation (mL)	293.0	(251.8 - 375.5)	242.5	(161.5 -361.0)
Maximum cystometric capacity (mL)	430	(300.5 - 607.0)	529.0	(470.8 - 609.8)

Values are presented as frequency (percentage), or as median (Q1-Q3).

*: excluding patients under supra-pubic catheter

NOUR: Non-obstructive urinary retention; **SNM:** Sacral nerve modulation; **CISC:** Clean intermittent self-catheterization; **IPG:** Implantable pulse generator

PART III

AFTER THERAPY INITIATION,

QUESTIONING THE FOLLOW-UP

REAL-LIFE AFTER SACRAL NERVE MODULATION IMPLANTATION: RATE, REASONS, AND RISK FACTORS FOR MID-TERM FOLLOW-UP DISCONTINUATION

Fifthly, we questioned the outcomes after sacral neuromodulation definitive implantation, particularly concerning the follow-up.

Efficacy and safety of sacral neuromodulation have already been extensively studied. However, to the best of our knowledge, no study has yet investigated follow-up after definitive implantation of the device. However, in view of the few "real-life" data published, including a high rate of loss of efficacy - which may necessitate a revision of the device, a modification of settings and/or the addition of a concomitant treatment - it now seems more important than ever to question patients' follow-up, to ultimately develop more appropriate care pathways.

This retrospective study was published in the journal *Progrès en Urologie* in 2023 (158).

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ABSTRACT

Objectives: To evaluate follow-up after implantation of a sacral nerve modulation implantable pulse generator (IPG) and to investigate the reasons and risk factors for follow-up discontinuation.

Methods: All patients who underwent an IPG implantation to treat lower urinary tract symptoms between 2014-2019 within 6 hospital centers located in the district of "Hauts-de-France" (France) were systematically called during the year 2020 for a standardized (tele)consultation. Patients were divided into 3 distinct profiles according to the regularity of their 5-year postoperative follow-up: "Regular follow-up", "Irregular follow-up" and "Lost to follow-up". The primary outcome was the change in the annual proportion of the 3 follow-up profiles over the 5 years following IPG implantation. As secondary outcomes we described the reasons reported for follow-up discontinuation and looked for risk factors associated with.

Results: Overall, 259 patients were included. At the time of data collection, after a mean follow-up of 28.4 (±19.8) months, 139 patients (53.7%) had a "Regular follow-up", 54 (20.8%) had an "Irregular follow-up" and 66 (25.5%) were "Lost to follow-up". The proportion of patients with a "Regular follow-up" decreased year by year, representing only 46.2% of patients at five-years. 175 patients (67.6%) underwent a standardized (tele)consultation. In multivariate analysis, only "lack of knowledge of the follow-up protocol" was statistically associated with follow-up discontinuation (OR = 5.16; 95% CI [2.12-13.57]).

Conclusion: The proportion of patients followed up after IPG implantation decreased steadily over the years, often related to a lack of therapeutic education.

INTRODUCTION

Sacral nerve modulation (SNM) is recommended as a second to third-line treatment for overactive bladder syndrome (OAB) and as an alternative to clean intermittent self-catheterization for non-obstructive urinary retention (NOUR) [*1,2]*. Sacral nerve modulation can also be discussed in the management of chronic bladder pain syndrome (CBPS) [3].

Sacral nerve modulation implantable pulse generator (IPG) implantation is subjected to a test period to evaluate whether the therapy provides adequate symptom relief. This staged strategy includes an initial surgical procedure to implant a unilateral lead close to the sacral root (often S3) using a trans-cutaneous approach. The lead is then connected to an external electrical generator for a period of 2 to 4 weeks. Today, it is consensually accepted to proceed with IPG implantation if patient achieves ≥ 50% improvement in one or more of his bothersome urinary parameters. The success rate of this staged trial varies depending on the indication, ranging from 51%-80% for OAB [2,4-7] and from 56%-68% for NOUR [2,8].

Although clinical randomized trials [9,10] have demonstrated stable efficacy, several prospective and retrospective real-life studies have consistently reported a decrease in the efficacy of SNM over time. For example, Hernandez-Hernandez et *al* [11]. and Janssen et *al* [12]. reported a loss of efficacy of the therapy in 28.5% and 32.0% of cases, after 61.4 months and 85.0 months of follow-up, respectively. Similarly, Elhilali et *al.* reported a maintenance of the efficacy of the therapy in only 45.0% of patients 3 years after IPG implantation [13]. These losses of efficacy may require a modification of the settings, a surgical revision, or the addition or change of another treatment. In addition, complications and side effects are frequent, estimated between 30.0% and 42.0% during an average follow-up of 6 to 24 months [4-7,14,15], and may require surgical revision in nearly one third of patients [4]. A strict, regular, and prolonged follow-up seems therefore necessary. This position is supported by the French National Agency for the Safety of Medicines and Health Products (ANSM), which considers the IPG to be an active implantable medical device, in the same way as cardiac defibrillators (AEDs) [16]. It should therefore, after implantation, be subject to a strict follow-up protocol as proposed by the French National Authority for Health (HAS) [17], including a systematic consultation at 1 month, 3 months and then annually, regardless of any intercurrent event. However, even if the recommendations are clear, compliance with this follow-up protocol has never been evaluated in real life.

The present study aims to evaluate the mid-term follow-up after IPG implantation for urological indications and to investigate the risk factors for follow-up discontinuation.

METHODS

Study Design

During the year 2020, six French secondary and tertiary hospital centers (1 university hospital center, 4 secondary public hospital centers, 1 private hospital), all located in the district of "Hauts-de-France" (France), standardized their practices regarding patient follow-up after IPG implantation. As part of this process, all patients who were implanted with an IPG for a lower urinary tract symptom - OAB, NOUR and/or CBPS - between January 1, 2014 and December 31, 2019 were called for a standardized (tele)consultation, either as part of their usual follow-up, or as part of a follow-up resumption - if they were considered as lost to follow-up by their implanting center.

All patients included in this pathway were eligible for the present study. They were divided according to the regularity of their 5-year postoperative follow-up after IPG implantation, allowing to define 3 distinct follow-up profiles: 1) "Regular follow-up" - patients who attended all follow-up visits as recommended by the HAS; 2) "Irregular follow-up" - patients who attended only part of the follow-up visits, but who attended the last follow-up visit(s); 3) "Lost to follow-up" - patients who discontinued follow-up and subsequently did not attend any of the follow-up visits (apart from the visit re-scheduled for a standardized (tele)consultation). A patient was considered to have attended a follow-up visit if he/she was reviewed by his/her referring urologist (or representative) on the anniversary date of implantation ± 6 months. In case of IPG removal within the 5 years of implantation, the patient was systematically censored at the time of explant.

Outcomes of interest

The primary outcome was the change in the annual proportion of the 3 follow-up profiles ("Regular follow-up"; "Irregular follow-up"; "Lost to follow-up") over the 5 years following IPG implantation.

As secondary outcomes we described the reasons reported for follow-up discontinuation and looked for risk factors associated with. We also described the reasons reported for follow-up resumption, if any.

Reasons for follow-up discontinuation were collected from patients with "Irregular Follow-up" or "Lost to Follow-up" profile during the standardized (tele)consultation, based on a pre-established 14-proposition list (Supplementary Table 1). Reasons for follow-up resumption were collected from patients with "Irregular follow-up" profile during the standardized (tele)consultation, based on a pre-established 9-proposition list (Supplementary Table 2). To seek for risk factors for follow-up discontinuation we compared patients considered as having "Irregular Follow-up" or being "Lost to Follow-up" to patients having "Regular Follow-up" 3 years after IPG implantation. Risk factors sought included the presence of a chronic disease, socio-professional category, level of education, and European Deprivation Index (EDI) score at the time of IPG implantation. The presence of a chronic disease was determined by the existence of at least one of the 30 long-term illnesses (ALD30) defined by the French public health insurance system giving the right to an exemption from co-payment. The socio-professional category was defined according to the INSEE (National Institute of Statistics and Economic Studies) nomenclature of professions and socio-professional categories (PCS) [18]. The level of education was defined according to the French classification of education levels of the INSEE [19]. The EDI score is a "cross-cultural" ecological indicator of socio-economic level, scored from 1 to 5 (poverty score >3) calculated from data in the European Union Statistics on Income and Living Conditions register [20,21].

Statistical analysis

Qualitative variables were described in terms of frequencies and percentages. Quantitative variables were described by the mean and standard deviation or by the median and interquartile range in case of a non-Gaussian distribution. The normality of the distributions was previously checked graphically and using the Shapiro-Wilk test. The frequency of patients who had a complete follow-up within 5 years after NMS implantation was calculated with its 95% confidence interval. The search for risk factors for irregular follow-up or loss to follow-up at 3 years was performed by a logistic regression model. Factors associated with the 0.05 threshold in univariate analyses were entered into a multivariate logistic regression model.

The significance level was set at 0.05. Statistical analyses were performed using SAS software (SAS Institute version 9.4).

RESULTS

Patients' characteristic

Within the 6 participating hospital centers, 259 patients (Table 1) with a mean follow-up of 28.4 (±19.8) months were assessed, including 139 (53.7%) considered as having a "Regular follow-up" profile, 54 (20.8%) as having an "Irregular follow-up" profile and 66 (25.5%) as having a "Lost to follow-up" profile. Among them, 175 were admitted to a standardized (tele)consultation after a mean follow-up of 28.4 (±19.4) months, including 105 patients (60.0%) with "Regular follow-up" profile, 34 (19.4%) with "Irregular follow-up" profile and 36 (20.6%) with "Lost to follow-up" profile (Figure 1). All implanted devices were Interstim II (Medtronic®, Minneapolis, Minnesota, USA). The lead was implanted at the S3 root level in 252 patients (97.1%). Overall, fifty patients (19.4%) had at least one early postoperative complication. Over the follow-up period, 67 IPGs (25.9%) were explanted and 13 (5.0%) were switched off (Supplementary Table 3).

At the time of IPG implantation, 221 patients (87.0%) considered themselves greatly or very much improved. At the time of standardized (tele)consultation, 47/105 patients (45.1%) considered has having a "Regular follow-up" reported a decrease or even a complete loss of effectiveness of their IPG. Among patients considered as having an "Irregular follow-up" or as being "Lost to follow-up" they were 16/34 (48.1%) and 11/36 (31.1%), respectively. Among them 53/175 patients (30.3%) were taking a urological treatment concomitant with the SNM. Patients considered as having a "Regular follow-up" or an "Irregular follow-up" or considered as being "Lost to follow-up" reported to be aware of the follow-up protocol in 83.3%, 57.1% and 40.5% of cases, respectively. In addition, 54.5% of patients reported that they never received a call from their implanting center for their follow-up visits.

Outcomes of interest

Primary outcome

During the 5-year follow-up period after IPG implantation, the proportion of patients with a "Regular follow-up" profile decreased year after year. Five years after IPG implantation, 46.2% of patients were considered as having "Regular follow-up" profile; 15.4% and 38.5% were considered to have "Irregular follow-up" and "Lost to follow-up" profiles, respectively (Figure 2).

Secondary outcomes

Reasons for follow-up discontinuation

Of the 120 patients considered as having "Irregular follow-up" or being "Lost to follow-up", 70 (58.3%) eventually presented for a standardized (tele)consultation. When asked about the reasons for follow-up discontinuation, the 3 main reported reasons were: 1) lack of discomfort related to urinary symptoms (26.5%); 2) lack of time due to other health constraints (22.1%); 3) lack of knowledge about other treatment options (13.2%) (Figure 3).

Reasons for follow-up resumption

Of the 54 patients considered as having "Irregular follow-up", 34 (63.0%) finally presented for a standard (tele)consultation. When asked about the reasons for follow-up resumption, the 3 main reported reasons were: 1) occurrence of an IPG dysfunction (41.2%); 2) occurrence of an IPG-related complication (11.8%); 3) occurrence of another urological problem (11.8%) (Supplementary Figure 1).

Risk factors for follow-up discontinuation

In univariate analysis, active smoking ($p<0.02$), number of dependent children >2 ($p=0.04$), and lack of knowledge of the follow-up protocol ($p<0.0001$) at the time of IPG implantation

were statistically associated with the occurrence of follow-up discontinuation at 3 years post-implantation. In multivariate analysis, only lack of knowledge of the follow-up protocol was statistically associated with follow-up discontinuation (OR=5.16; 95% CI [2.12-13.57]) (Supplementary Table 4).

DISCUSSION

While the indications and the implantation technique of SNM are now well established [22], the same cannot be said for follow-up after IPG implantation. Indeed, given the loss of efficacy and potential complications that may arise afterwards, follow-up after IPG implantation seems essential. To date, it has been the subject of only one simple proposal from the HAS. In this document, written in 2010, the HAS proposed systematic consultations at 1 month, 3 months and then annually, regardless of any intercurrent event. To our knowledge, no other specific recommendation has yet been published worldwide.

In the present study, we reported a progressive decrease over the years in the proportion of patients followed-up after IPG implantation. Thus, at 5 years, more than half of the patients had discontinued their follow-up at some point, and sometimes permanently. Reassuringly, 42.9% of these patients did not consider themselves sufficiently inconvenienced to resume follow-up; and 43.0% of patients who returned on their own did so because of complications or dysfunction of the IPG. These data suggest that most patients who are out of follow-up will contact their implanting center if necessary. This should however not obscure more worrying data. Indeed, one third of the patients that were considered as being lost to follow-up reported a partial or complete loss of efficacy of the IPG and one quarter could not operate the remote control by themselves. In addition, 5.7% and 7.1% of these patients reported conflicting with their implanting center or having failed to make an appointment.

The data from the present study, including loss of efficacy in 42.1% of cases as well as revision and explant rates of 28.2% and 25.9%, remind us of the importance of regular follow-up after IPG implantation. This follow-up must allow us to evaluate the efficacy and proper functioning of the IPG. It is important to note the lower proportion of patients lost to follow-up with concomitant urological treatment (23.8%), compared to patients who attended all the postoperative visits (35.5%), which is probably due to a lower therapeutic adjustment in patients who are not regularly followed up.

Lack of compliance with follow-up was often related to a lack of therapeutic education. Indeed, among the patients lost to follow-up, only 40.5% felt they had been informed of the need for annual follow-up and a total of 24.3% of patients were unaware that other therapies could be offered to them. Moreover, lack of knowledge of a specific follow-up protocol after IPG implantation appeared as the only risk factor for follow-up discontinuation in multivariate analysis (OR = 5.16; 95% CI [2.12-13.57]).

Furthermore, considering that more than half of the patients reported that they had not received any call from their implanting center for their follow-up visits, and that follow-up discontinuation was reported to be caused in 10% of cases by "departure of the referring urologist", "conflictual relationship with the center" or "impossibility of making an appointment", we can estimate that the conditions for ensuring adequate postoperative follow-up did not always seem to be met.

The setting up of a therapeutic education time and a long-term follow-up protocol requires the implanting centers to think about the care pathway and to make available human resources dedicated to this activity. In this context, the development of teleconsultation, the use of web-based remote monitoring interfaces and the delegation of monitoring to paramedical staff are all interesting ways to explore. Teleconsultation is now booming and the tools necessary for its implementation are now easily accessible. A review of the literature on teleconsultation in urology reported the organizational and financial advantages of this approach, which limits unnecessary travel and the duration of consultations, while ensuring regular clinical follow-up [23]. In parallel with teleconsultation, the concept of a web interface through which follow-up could be automated has recently appeared. This type of tool has been proposed after hip surgery, with the aim of redeploying limited human resources from post-operative follow-up to the management of new patients. Thus, in a study of 41 patients followed up for 12 months, Marsh et *al.* reported encouraging results with almost complete data collection and systematic detection of patients presenting a postoperative complication [24]. In our study, almost one third of patients who had follow-up discontinuation reported time constraints as the main reason, making these web interfaces promising tools. It would therefore be interesting if the patient remote control supplied by Medtronic® could provide a suitable follow-up procedure, including reassessment consultations, associated with the use of auto-questionnaires to check for complications, malfunctions, or loss of efficiency. However, neither the teleconsultation nor the web interface allows to interrogate the IPG nor

to modify the settings. This would require the rapid organization of a face-to-face consultation in case of loss of efficacy and/or complications. Delegation of the follow-up to paramedical staff would probably make it possible to meet this limitation, while sparing medical resources. In an observational study of 1526 patients, Van Eck et *al.* reported that patient follow-up and evaluation of AEDs was performed in 95% of cases by trained "technicians" and that only 10% of consultations required the intervention of the cardiologist [25]. In France, the emergence of Advanced Practice Nurses (APNs) could help build efficient care pathways, while preserving medical resources that could be directed towards the management of more complex cases.

The main limitation of the present study lies in the collection of data, which was only completely obtained for 175 patients (67.6%) and on a declarative basis during a standardized (tele)consultation. In addition, the collection of a certain amount of information was based on old memories, leaving considerable place for memory and/or interpretation bias. Although we were able to report SNM-related complications, lead and/or IPG revisions and explant, we were unable to report information on setting adjustments, which were rarely specified in medical records. The explant rate reported here (25.9%) seems higher than that previously reported in the literature (15%-19. 1 %)[6,7]. It is important to note, however, that most of these patients were implanted for non-neurogenic OAB. In our study, over 40% of patients were implanted for another indication - including 30.6% for NOUR and 10.5% for CBPS - and 29.1% had an underlying neurological disease. It is in these indications that SNM appears to be the least effective. Bearing in mind that most patients explanted (53.7%) were for loss of efficacy, it seems reasonable to think that the difference in indications for SNM may explain, at least in part, this high explant rate. In order to study the causes and risk factors of discontinuation of follow-up, we decided to group together patients with an "Irregular follow-up" profile and a "Lost to follow-up" profile. These two groups, whose homogeneity remains questionable, nevertheless allowed us to increase the number of events reported. Concerning the study of risk factors for follow-up discontinuation, we decided to take a "middle ground" approach at 3 years after IPG implantation. Indeed, looking for these risk factors for discontinuation of follow-up earlier or later would have exposed us to a loss of power, with either few patients in follow-up discontinuation (1 year: 42/234 patients), or few patients in total (5 years: 91 patients). Furthermore, it is plausible to consider that the efficacy of SNM might have an impact on follow-up discontinuation. Nevertheless, the study design, which involved a standardized efficacy evaluation after a mean follow-up of 28.4 (±19.4) months,

with the search for risk factors carried out 3 years post-implantation, did not allow us to carry out such analysis. Beyond these limitations and methodological discussion points, it is important to recall that the present study is the first to specifically investigate mid-term follow-up after IPG implantation beyond the usual simple considerations of efficacy and safety.

CONCLUSION

Despite a loss of efficacy and frequent side effects, the proportion of patients followed up after IPG implantation decreases regularly over the years, reaching barely 50% at 5 years. The lack of therapeutic education and the absence of a care pathway dedicated to this follow-up seem to explain, at least in part, these numerous discontinuations.

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Figure 1: Flow Chart

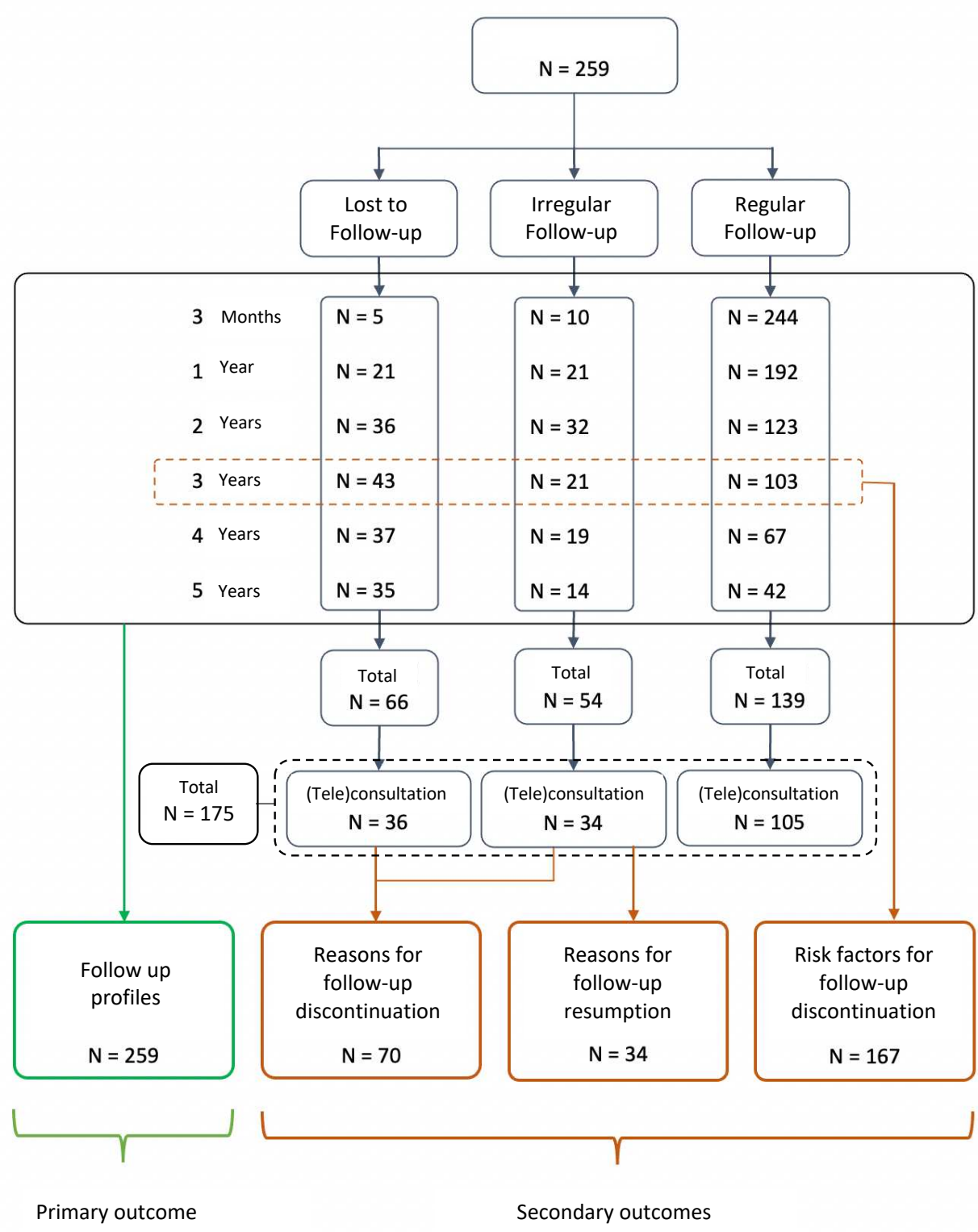


Table 1: Patients' characteristics

	N = 259	
Age, years (mean ± SD)	59.0	± 14.4
Gender		
Female	214	(83.0)
Body mass index, kg/m^2 **(**mean ± SD)	28.0	± 6.3
Indication for SNM		
Dry OAB	71	(72.5)
Wet OAB	160	(62.0)
NOUR	79	(30.6)
CBPS	27	(10.5)
Voiding mode		
Spontaneous voiding	212	(82.2) (
Clean intermittent self-catheterization	34	13.2)
Third-person catheterization	7	(2.7)
Indwelling catheter	4	(1.6)
On-going concomitant urological treatments		
Anticholinergics	45	(17.2)
Alpha-blockers	41	(16.0)
B3-adrenergics	1	(0.4)
Intravesical injections of botulinum toxin a	2	(0.8)
Marital Status		
Single	29	(14.1)
Married	132	(64.1)
Cohabiting	14	(6.8)
Divorced or widowed	31	(15.0)
Number of dependent children	2.2	± 1.6
Level of education		
< Middle school graduation	74	(37.9)
Middle school graduation	45	(23.1)
High school graduation	21	(10.8)
Bachelor's degree	15	(7.7)
Master's degree	40	(20.5)
Professional status		
Farmers	1	(0.5)
Craftsmen, merchants, and company managers	8	(3.8)
Executives and higher intellectual professions	17	(8.0)
Intermediate professions	18	(8.5)
Employees	50	(23.6)
Workers	9	(4.2)
Retired	56	(26.4)
No professional activity	51	(24.1)
Student	2	(0.9)
EDI-score (mean ± SD**)**	4.2	± 1.3
≧ 1 Chronic pathology (ALD30)	185	(74.3)
Underlying neurological disease		
No underlying neurological disease	183	(70.9)
Multiple sclerosis	18	(7.0)
Spina cord injury	8	(3.1)
Spina bifida	0	(0.0)
Cerebral lesion	17	(6.6)
Parkinson's syndrome	10	(3.9)
Other neurological pathology	18	(7.0)
Multiple neurological disease	4	(1.5)
Addictive behaviors		
No addictive behavior	138	(59.7)
Tobacco	49	(21.6)
Medication	55	(23.9)
Alcohol	16	(7.1)
Others	10	(4.6)
Distance between home and hospital, km (mean ± SD)	29.2	± 35.9

All values are presented in frequency (percentage), unless otherwise indicated.
OAB: Overactive bladder; **NOUR:** Non-obstructive urinary retention; **CBPS:** Chronic bladder pain syndrome**; EDI:** European Deprivation Index**; ALD30:** long-term illnesses giving right to exemption from co-payment by French public health insurance

Figure 2: Evolution of the proportion of follow-up profiles during the 5 years following IPG implantation

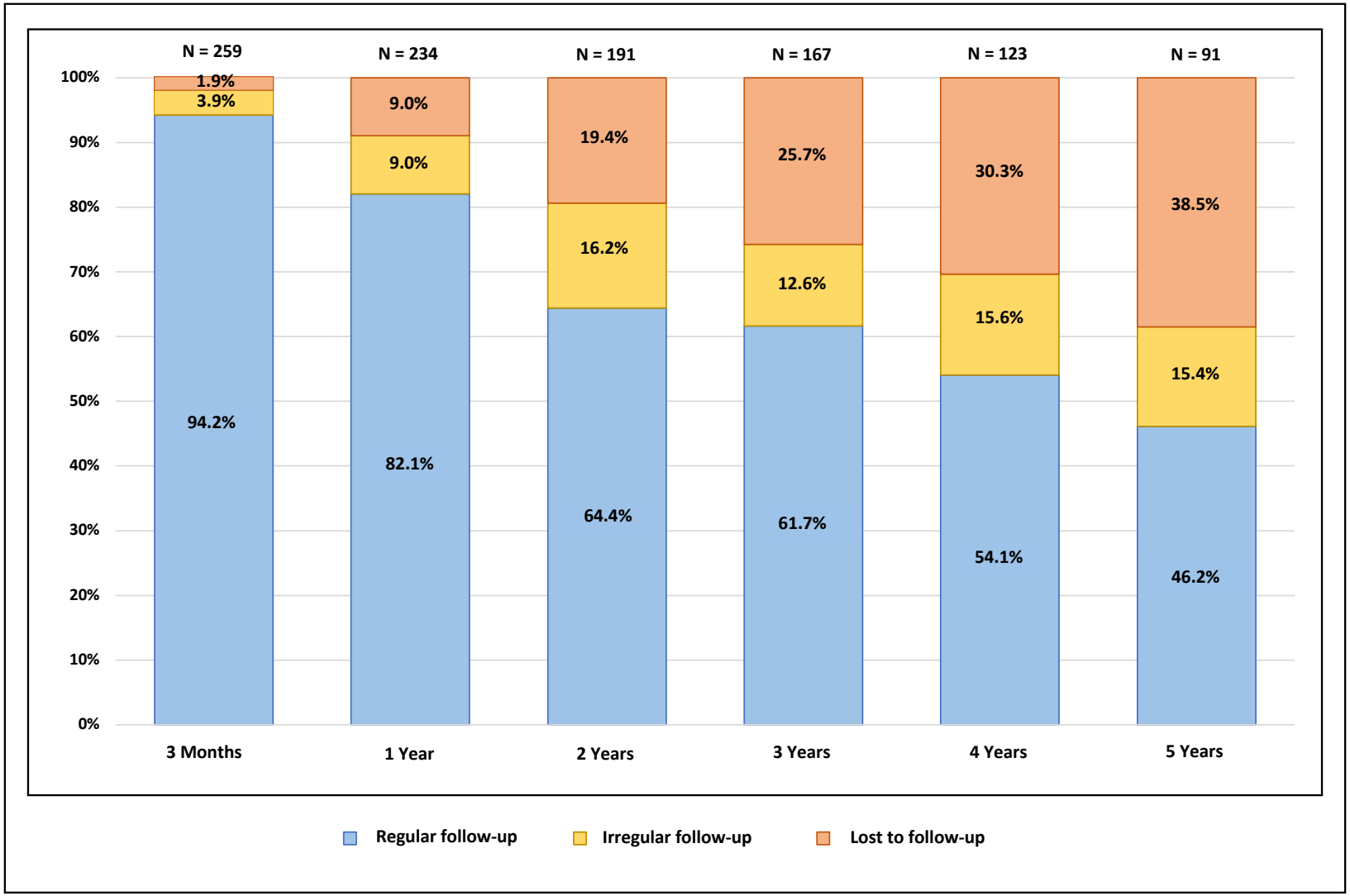
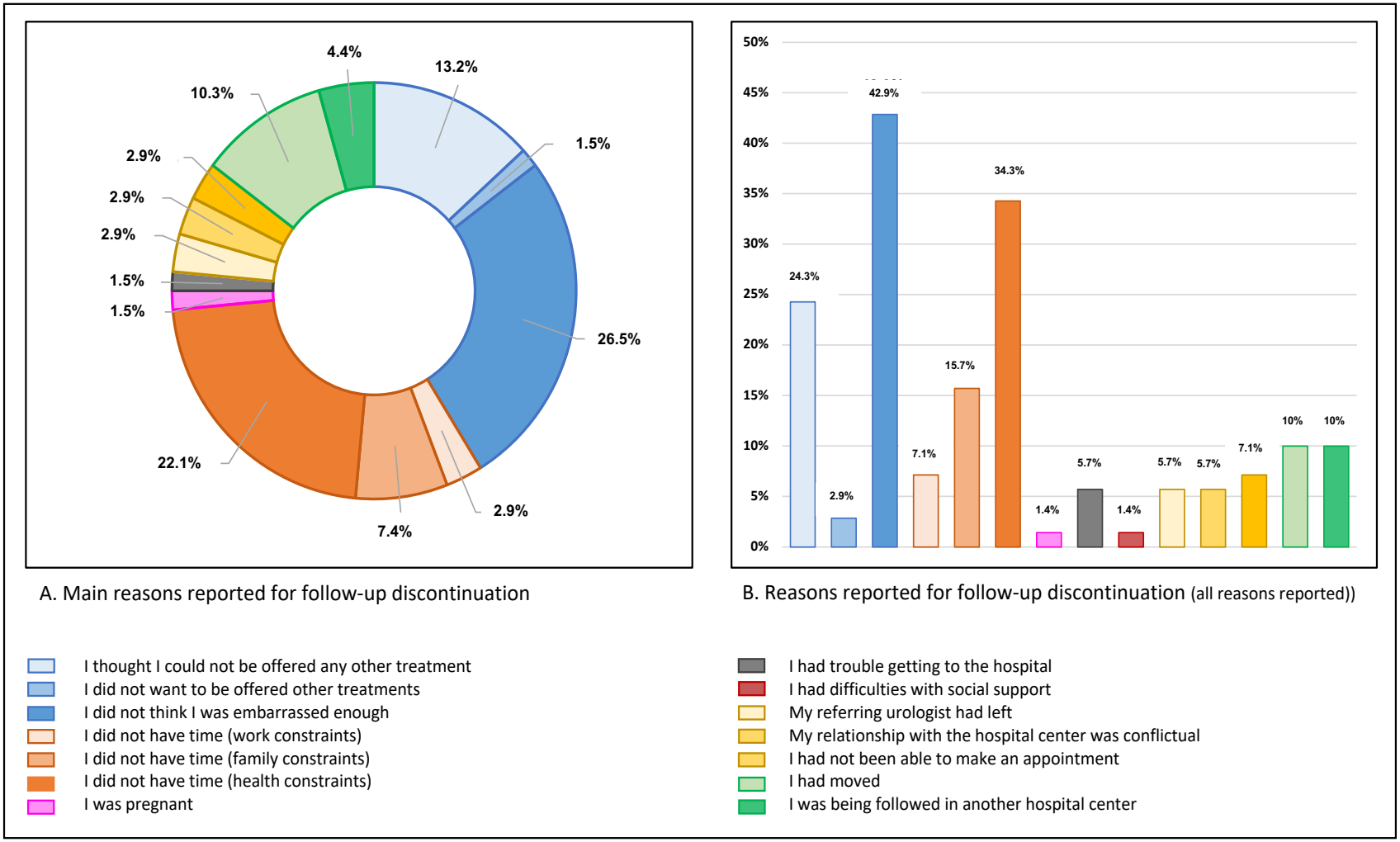


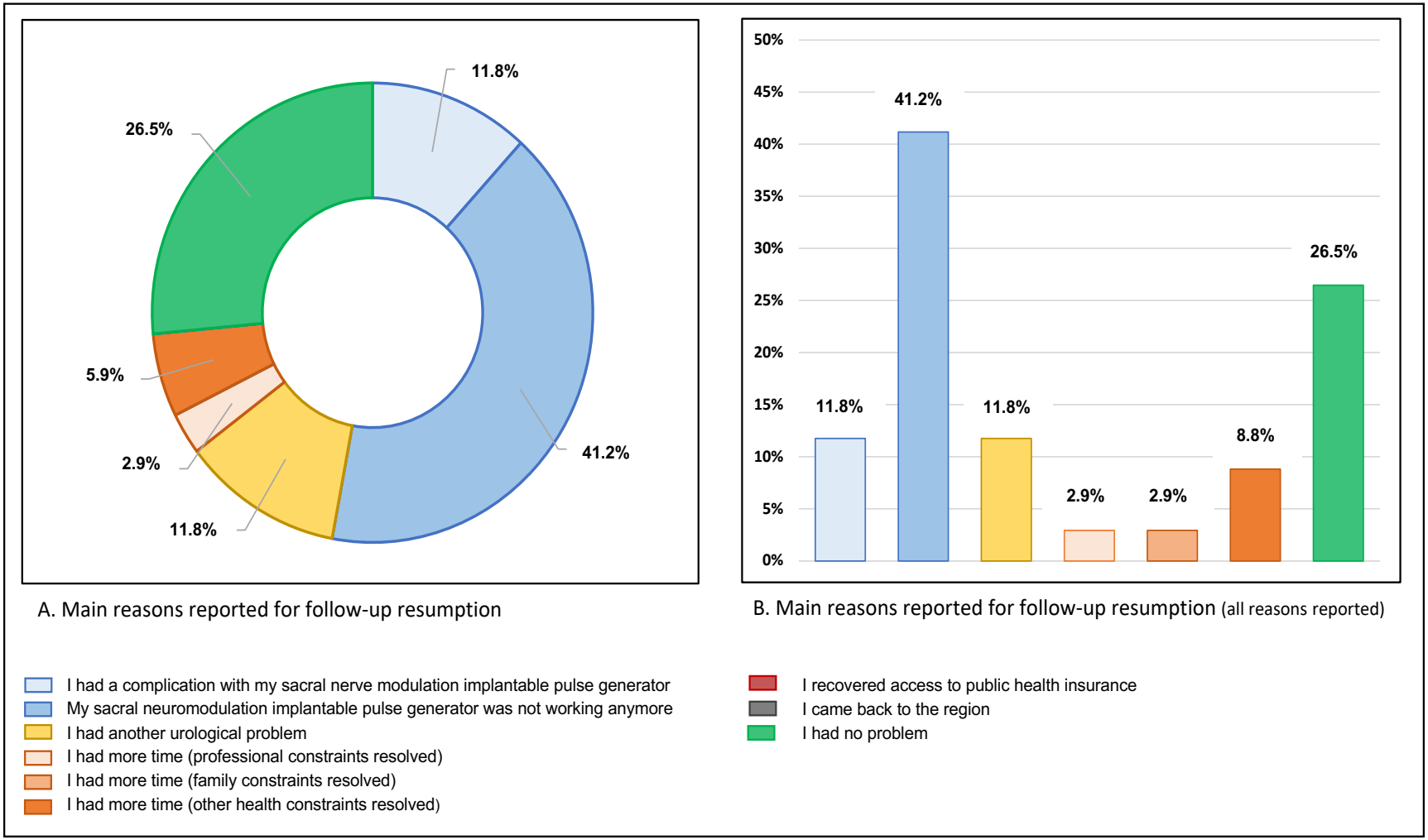
Figure 3: Reasons for follow-up discontinuation



A. Main reasons reported for follow-up discontinuation

B. Reasons reported for follow-up discontinuation (all reasons reported))

Supplementary Figure 1: Reasons for follow-up resumption



A. Main reasons reported for follow-up resumption

B. Main reasons reported for follow-up resumption (all reasons reported)

Supplementary Table 1: Pre-established list of reasons for follow-up discontinuation

List of propositions
1. I thought I could not be offered any other treatment.
2. I did not want to be offered any other treatment.
3. I didn't think I was embarrassed enough.
4. I didn't have time (work constraints).
5. I didn't have time (family constraints).
6. I didn't have time (health constraints).
7. I was pregnant.
8. I had trouble getting to the hospital.
9. I had difficulties with getting public health insurance.
10. My referring urologist had left.
11. My relationship with the hospital center was conflictual.
12. I had not been able to make an appointment.
13. I had moved.
14. I was being followed in another hospital center.

Supplementary Table 2: Pre-established list of reasons for follow-up resumption

List of propositions
1. I had a complication with my sacral nerve modulation implantable pulse generator.
2. My sacral neuromodulation implantable pulse generator was not working anymore.
3. I had another urological problem.
4. I had more time (professional constraints resolved).
5. I had more time (family constraints resolved).
6. I had more time (other health constraints resolved).
7. I recovered acess to public health insurance.
8. I came back to the region.
9. I had no problem.

Supplementary Table 3: Explant, switching off and revision of the SNM device

	N = 259	
Explant of the SNM device	67	(25.9)
Average time to explant, months (mean ± SD)	20.0	± 17.3
Reason for explant		
Don't know	7	(10.4)
Infection	18	(26.9)
Stimulation-related pain	4	(6.0)
Bread site layout	2	(3.0)
Loss of efficacy	36	(53.7)
Switching Off the IPG	13	(5.0)
Average time to turning Off, months (mean ± SD)	21.9	± 17.8
Reason for turning Off		
Don't know	3	(23.1)
Stimulation-related pain	2	(15.4)
Bread site layout	1	(7.7)
Loss of efficacy	5	(38.4)
Pregnancy	2	(15.4)
Surgical revision of the lead and/or IPG	73	(28.2)
Average time to revision, months (mean ± SD)	24.5	± 20.2
Reason for revision		
Don't know	11	(15.1)
Revision of the lead	10	(13.7)
Change of IPG for dysfunction	23	(31.6)
Change of IPG for battery depletion	17	(23.2)
Change of the lead and the IPG	11	(15.1)
Other	1	(1.3)

All values are presented in frequency (percentage), unless otherwise indicated.

SNM: Sacral nerve modulation; **IPG:** Implantable pulse generator

Supplementary Table 4: Risk factors for follow-up discontinuation (univariate and multivariate analysis)

	Univariate analysis			Multivariate analysis		
	OR	**95% CI**	**p**	**OR**	**95% CI**	**p**
Age						
≧ 60 yo *vs* 60 yo	1.67	0.88-3.15	0.12	-	-	-
Gender						
Woman *vs.* Man	1.00	0.42-2.37	0.99	-	-	-
Marital status						
Single vs Married	1.16	0.38-3.51		-	-	-
Concubine vs Married	1.38	0.40-4.74	0.65	-	-	-
Divorced/Widowed vs Married	1.93	0.69-5.40		-	-	-
Number of dependent children						
≦ 2 vs >2	2.19	1.05-4.56	0.04	2.05	0.79-5.33	0.14
Level of education						
Upper than High school graduation *vs* High school graduation or lower	1.30	0.60-2.82	0.50	-	-	-
Professional status *						
Lower socio-professional categories *vs* Upper socio-professional categories	1.21	0.43-3.44	0.90	-	-	-
Not working + Retired + Student *vs* Upper socio-professional categories	1.17	0.43-3.14		-	-	-
EDI score						
1 *vs* 4	1.60	0.23-11.26	0.76	-	-	-
2 *vs* 4	3.20	0.54-18.97		-	-	-
3 *vs* 4	2.13	0.33-13.81		-	-	-
5 *vs* 4	1.63	0.41-6.54		-	-	-
Distance between home and hospital						
< 5 km *vs* > 35 km	1.62	0.59-4.48		-	-	-
5-15 km *vs* > 35 km	1.61	0.67-3.84	0.72	-	-	-
15-35 km *vs* > 35 km	1.33	0.53-3.36		-	-	-
≧ 1 Chronic pathology (ALD30)						
Yes *vs* No	1.22	0.60-2.50	0.58	-	-	-
Underlying neurological disease						
Yes *vs* No	1.68	0.84-3.35	0.14	-	-	-
Addictive behaviors						
Yes *vs* No	1.71	0.87-3.37	0.12	-	-	-
Alcohol vs No	1.07	0.30-3.83	0.92	-	-	-
Tobacco vs No	2.48	1.14-5.40	0.02	1.99	0.699-5.63	0.20
Medication vs No	1.06	0.49-2.29	0.89	-	-	-
Indication for SNM						
Dry OAB *vs* No	1.10	0.55-2.20	0.78	-	-	-
Wet OAB *vs* No	1.24	0.64-2.38	0.52	-	-	-
NOUR vs No	1.45	0.70-2.96	0.31	-	-	-
CPBS vs No	1.46	0.53-4.00	0.46	-	-	-
Perioperative complication						
Yes *vs* No	1.52	0.62-3.73	0.36	-	-	-
Knowledge of the monitoring protocol						
Yes *vs* No	6.37	2.60-15.64	<0.001	**5.36**	**2.12-13.57**	**<0.001**

***Lower socio-professional:** farmers, intermediate professions, employees, workers**; Upper socio-professional categories**: craftsmen, shopkeepers and company managers, higher intellectual professions

EDI: European Deprivation Index**; ALD30:** long-term conditions giving right to exemption from co-payment by health insurance**; OAB:** overactive bladder; **NOUR:** Non-obstructive urinary retention; **CPBS:** Chronic bladder pain syndrome

CONCLUSION

AND PROSPECTS

I. CONTRIBUTIONS OF THE THESIS

I.1 Before therapy initiation, questioning the indication

In the present thesis, we have first synthesized the scientific literature on early interventions to prevent the emergence of lower urinary tract dysfunctions due to spinal cord injury. The high number of studies reporting significant improvement in urodynamic parameters clearly supports the concept of a preventive approach aimed at interfering with anarchic sub-lesional reorganization, at least in certain animal models. Electrical stimulation/modulation therapies - accounting for 9 studies, including 1 in humans - are the therapeutic approaches for which we have the most data. Recent findings also suggest that modulation of neuronal activity may activate plasticity-related growth mechanisms and increase collateral sprouting, thereby enhancing the functional effect of axonal remodeling. Moreover, although electrical stimulation has long been known to enhance peripheral axon regeneration, it has recently been reported that electrical modulation can also enhance central nervous system plasticity in rodent models, as well as modulate and reinforce spared circuits in spinal cord injury patients. In view of these data, it seems reasonable to consider electrical stimulation/modulation therapies - primarily tibial neurostimulation as a minimally invasive approach - as preventive therapies in the near future, particularly in lower urinary tract dysfunctions due to spinal cord injury.

We also investigated the relationship, in terms of efficacy, between transcutaneous tibial neurostimulation and sacral neuromodulation. Our bi-centric retrospective study revealed a lack of statistical correlation between the two therapies, in terms of efficacy. These results will of course enable us to better support our patients as part of a shared decision making process. These results also raise questions about the mechanisms of action of electrical stimulation/modulation therapies. Although these two therapies target similar territories - S3 for sacral neuromodulation; L4-S3 for tibial neurostimulation - the lack of correlation in terms of efficacy suggests different mechanisms of action.

We have also developed the first predictive tool for definitive implantation of sacral neuromodulation in the context of voiding dysfunction. Based on 4 independent predictive

factors (3 clinical factors and 1 urodynamic factor), we established 16 response profiles with definitive implantation rates ranging from 8.7% - for the most unfavorable combination - to 81.5% for the most favorable combination. Although this new tool has been validated internally, it has yet to be validated externally. Nonetheless, we have been able to prove the feasibility of developing relevant predictive tools, which are essential to the deployment of shared decision making process.

I.2 At therapy initiation, questioning the mechanisms of action

In the present thesis we also evaluated changes in the balance of ANS in response to an acute sacral root acute stimulation. The results suggest that this acute stimulation can significantly influence ANS activity, including a notable increase in overall ANS activity associated with greater relative variability in PSNS. To better understand the significance of our results, it is important to note that they directly resonate with many of the previous findings concerning ANS abnormalities reported in the context of lower urinary tract dysfunction, and more specifically in OAB/UUI. Recent studies suggest abnormally high SNS activity in this pathological context. Thus, we hypothesized that sacral neuromodulation could improve OAB/UUI, and perhaps other types of lower urinary tract dysfunctions, by "rebalancing" the ANS, increasing PSNS activity and counteracting SNS hyperactivity.

I.3. After therapy initiation, questioning the follow-up

We finally evaluated the medium-term follow-up (5 years) after definitive implantation of sacral neuromodulation in a geographic population pool, looking for risk factors for discontinuation of follow-up. Despite loss of efficacy and frequent side-effects, the proportion of patients followed-up after definitive implantation of sacral neuromodulation declined steadily over the years, reaching barely 50% at 5 years. A third of patients considered lost to follow-up reported partial or total loss of efficacy of sacral neuromodulation, and a quarter could no longer operate the remote control on their own. The only risk factor identified in this study was lack of therapeutic education. In France, the recent emergence of Advanced Practice Nurses could make it possible to build efficient care pathways, while preserving medical resources that could be directed towards the management of more complex cases. In

addition, the development of digital interfaces could support follow-up care, with the use of online self-assessments to look for complications, malfunctions and/or loss of efficacy.

II. RESEARCH PROSPECTS

Based on what we have been able to report in the introduction, and in view of the results reported in the present thesis, future work on the optimization of electrical stimulation/modulation therapies should be developed along the following lines:

Focus 1: Identify the indications and populations most likely to benefit, by:

- Evaluating the short, medium and long-term clinical and urodynamic efficacy of tibial neurostimulation and sacral neuromodulation in specific neurological and non-neurological populations as a treatment for OAB/UUI and voiding dysfunction.
- Evaluating the short, medium and long-term clinical and urodynamic efficacy of tibial neurostimulation as a treatment for voiding dysfunction in neurological and non-neurological populations.
- Developing predictive tools for the success of tibial neurostimulation and sacral neuromodulation as treatments for OAB/UUI and voiding dysfunction.
- Confirming the efficacy of tibial neurostimulation and sacral neuromodulation as preventive treatments in certain specific indications, in relation to their probable effect on neuroplasticity.

Focus 2: Clarify acute and chronic mechanism(s) of action, at the level of the central nervous system and autonomic nervous systems, by:

- Confirming and refining results relating to changes in brain activity and connectivity - in the short, medium and long term - in connection with tibial neurostimulation and sacral neuromodulation, as a treatment for OAB/UUI and voiding dysfunction.
- Confirming and refining the changes in ANS activity associated with tibial neurostimulation and sacral neuromodulation - in the short, medium and long term - as a treatment for OAB/UUI and voiding dysfunction.

Focus 3: Specify setting strategy - at baseline and in the event of loss of efficacy, by:

- Evaluating different initial setting strategies (pulse rate, pulse duration, intensity, polarity, cycling) on efficacy, safety and battery life, for sacral neuromodulation, as a treatment for OAB/UUI and voiding dysfunction.
- Evaluating different setting strategies in the event of loss of efficacy (pulse rate, pulse duration, intensity, polarity, cycling) for sacral neuromodulation, as a treatment for OAB/UUI and voiding dysfunction.
- Evaluating different initial setting strategies (pulse rate, pulse duration, intensity, stimulation duration, stimulation period) on efficacy for tibial neurostimulation, as a treatment for OAB/UUI, and possibly for voiding dysfunction.
- Evaluating different setting strategies in the event of loss of efficacy (pulse rate, pulse duration, intensity, stimulation duration, stimulation period) for tibial neurostimulation, as a treatment for OAB/UUI, and possibly for voiding dysfunction.
- Evaluating different closed-loop conditional control strategies through afferent nerve activity analysis and ANS analysis.

Focus 4: Improve patient follow-up and promote treatment adherence, by:

- Investigating factors influencing patient adherence to treatment, such as ease of use of devices, management of side effects and overall patient satisfaction.
- Evaluating existing care pathways for patients receiving electrical stimulation/modulation and identifying critical points where improvements could be made.
- Designing and evaluating interventions to improve adherence to follow-up, including educational programs, remote follow-up tools and psychosocial support strategies.

It is also important to note that new electrical stimulation/neuromodulation therapies are currently emerging, such as transcutaneous peroneal neurostimulation, transcutaneous sacral neurostimulation and magnetic neurostimulation (159). The lines of research proposed above should also apply to these emerging therapies.

III. PROJECTS INITIATED AS A RESULT OF THE THESIS

Following the completion of this thesis, several research projects were initiated to address these different research areas.

Focus 1: Identify the indications and populations most likely to benefit, by:

- *Evaluating the short and medium-term clinical and urodynamic efficacy of sacral neuromodulation in MS as a treatment for OAB/UUI.*

  ⇒ The retrospective multicenter (Lille, Nantes, Rennes, Strasbourg) **MODULUSn** research protocol will evaluate the clinical and urodynamic efficacy of sacral neuromodulation as a treatment for OAB/UUI in MS patients. Data collection has already included 33 patients with a median follow-up of 20.4 months, including 13 patients with a follow-up of up to 5 years.

- *Evaluating the short-term clinical and urodynamic efficacy of tibial neurostimulation as a treatment for voiding dysfunction in MS.*

  ⇒ The randomized sham-controlled clinical trial entitled **NEUROSTIM-SEP1** will evaluate the clinical and urodynamic efficacy of transcutaneous sacral neurostimulation (12 weeks) as a treatment for voiding dysfunction in MS patients. The trial began in January 2022, and has already enrolled 34/68 patients, and is scheduled to run until December 2025. The protocol synopsis is presented in Appendix 1 (page 229).

- *Developing predictive tools of success for sacral neuromodulation as a treatment for voiding dysfunction.*

  ⇒ External validation of the predictive tool developed in this thesis is scheduled for 2024.

⇒ The multicenter retrospective trial (Europe and UK) entitled **2VOID** should make it possible to develop a more accurate and effective tool for predicting the success of sacral neuromodulation as a treatment for voiding dysfunction than that presented in the present thesis. Data collection should begin in 2024.

Focus 2: Clarify acute and chronic mechanism(s) of action, at the level of the central nervous system and autonomic nervous systems, by:

- *Confirming and refining findings on short-term changes in brain activity and connectivity - in relation to tibial neurostimulation as a treatment for OAB/UUI.*

⇒ The clinical trial entitled **STIMULUS** will evaluate changes in brain activity and connectivity before and after transcutaneous tibial neurostimulation (12 weeks) in MS patients. The trial is funded and scheduled to start in January 2025. The protocol synopsis is presented in Appendix 2 (page 233).

Rational for STIMULUS Trial

Multiple sclerosis (MS) is an inflammatory disease of the central nervous system. It mainly affects young women, with an average age at diagnosis of 30 and a male:female ratio of 1:4.

Lower urinary tract dysfunctions are one of the most frequent clinical manifestations (>80% of patients), including filling phase disorders associated with overactive bladder (OAB) – daytime frequency and nocturia - (26-82%) and/or urge urinary incontinence (UUI) (27-86%).

It has recently been reported that during bladder filling, patients with OAB/UUI show changes in the activity of brain structures involved in regulating the lower urinary tract (in terms of activity and connectivity), as well as changes in the regulation of the ANS.

In parallel, treatments for OAB/UUI, such as pelvic floor muscle contraction, anticholinergic therapy, intravesical injections of botulinum toxin A or sacral neuromodulation, appear to normalize - directly or indirectly - the activity of these brain structures, particularly the PAG - considered to be the main interface between the afferent and the efferent arms of the micturition.

Transcutaneous tibial neurostimulation is an electrical stimulation therapy involving the application of an electric current to the ankle. It is self-administered at home for 20 minutes a day. It has proved effective as a third-line treatment for OAB/UUI in MS patients, with significant improvement in urinary symptoms in the short term (12 weeks) in 83.3% to 89% of patients.

However, the mechanisms of action of tibial neurostimulation have not yet been clearly studied.

We therefore hypothesize that transcutaneous tibial neurostimulation administered as part of the treatment of OAB/UUI in MS patients could normalize the activity and connectivity of brain structures involved in regulating the lower urinary tract, as well as the activity of the ANS.

Study Design for STIMULUS Trial

This is a single-center, uncontrolled, prospective clinical trial involving a single group of patients, aimed at demonstrating an effect of tibial neurostimulation on the activity and connectivity of these brain structures, as well as on the activity of the ANS.

Patients will be recruited during neuro-urology consultations dedicated to the management of MS patients with lower urinary tract dysfunctions.

Once eligibility criteria have been verified and patients have given their consent, they will be included and begin transcutaneous tibial neurostimulation treatment for 12 consecutive weeks, for 20 minutes a day.

Included patients will be evaluated before and 12 weeks after initiation of transcutaneous tibial neurostimulation treatment, by means of:

- 3-day bladder diary
- Urinary symptom questionnaires (ICIQ-FLUTS, ICIQ-OAB, ICIQ-LUTSqol, QUALIVEEN)
- Urodynamic assessment combined with HRV during cystometry
- Structural and functional brain MRI, at rest and during continuous bladder filling using a dedicated urodynamic column.

Main objective for STIMULUS Trial

In patients with AVH/UTI in the context of MS, to evaluate the change in periaqueductal gray matter activity secondary to NSTP treatment.

Primary endpoint for STIMULUS Trial

Change in periaqueductal gray matter activation level at maximum cysto-manometric capacity after 12 weeks of NSTP treatment (difference between measurement before treatment (S0) and measurement after 12 weeks of treatment (S12).

Inclusion criteria for STIMULUS Trial

- Age over 18
- Female gender
- Multiple sclerosis
- OAB/UUI
- Failure, intolerance or contraindication to first-line treatment of OAB/UUI (anticholinergics)
- Written consent
- Socially insured
- Willing to comply with all study procedures and duration

Non-inclusion criteria for STIMULUS Trial

- Other associated neurological pathology
- Expanded Disability Status Scale (EDSS) score > 6 (< 3 months)
- Recurrent urinary tract infections (> 3 episodes / year)
- Bladder emptying disorders (RPM > 100ml and/or functional complaint)
- Associated stress urinary incontinence
- Anticholinergic treatment within the last month
- Beta-3 adrenergic treatment within the last month
- Alpha-blocker treatment within the last month
- Tibial neurostimulation within the last 3 months
- Sacral neuromodulation device in place and activated within the last 3 months
- Botulinum toxin A injection within the last 9 months
- Metal prosthesis in lower limb
- Non-MRI-compatible metal prosthesis
- Pacemaker
- Pregnancy in progress / Pregnancy project
- Guardianship / Curatorship

Number of subjects to include for STIMULUS Trial

The aim of the study is to demonstrate a significant variation (expected effect size >0.8 in terms of standardized difference) in the level of activation of periaqueductal gray matter at maximum cystometric capacity after 12 weeks of NSTP treatment. To demonstrate this large effect size of 0.8, with a two-sided test (alpha risk= 5%, power=90%), and considering 20% of non-analyzable patients (movement artifacts and lost to follow-up), it is necessary to include 24 subjects.

- *Confirming and refining the changes in ANS activity associated with short-term sacral neuromodulation - as a treatment for OAB/UUI.*

⇒ The **ESTIME** clinical trial will evaluate changes in ANS activity during acute sacral root stimulation in the context of sacral neuromodulation lead implantation for the treatment of OAB/UUI. It will be of particular interest in confirming the results reported in the present thesis. The trial is funded and scheduled to start in September 2024.

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ABBREVIATIONS

ACC: Anterior Cingulate Cortex

ANS: Autonomic Nervous System

CEN: Central Executive Network

CISC: Clean Intermittent Self-Catheterization

DMN: Default Mode Network

ECG: Electrocardiogram

fMRI: Functional Magnetic Resonance Imaging

HF: High Frequency

HRV: Heart Rate Variability

IPG: Implantable Pulse Generator

ICS: International Continence Society

lPFC: Lateral Prefrontal Cortex

LF: Low Frequency

MUI: Mixed Urinary Incontinence

MS: Multiple Sclerosis

OAB: Overactive bladder

PAG: Periaqueductal Gray Substance

PGI-I: Patient's Global Impression of Improvement

PET: Positron Emission Tomography

PMC: Pontine Micturition Center

PSNS: Parasympathetic Nervous System

RMSSD: Root Mean Square of the Successive Differences

SDNN: Standard deviation of all normal to normal R-R (NN) intervals

SMA: Supplementary Motor Area

SN: Salience Network

SNS: Sympathetic Nervous System

SPECT: Single-Photon Emission Computed Tomography

SUI: Stress Urinary Incontinence

UUI: Urinary Urgency Incontinence

UI: Urinary Incontinence

vmPFC: Ventromedial Prefrontal Cortex

APPENDIX 1: NEUROSTIM-SEP1 trial - Synopsis

PROMOTEUR	Centre Hospitalier Régional & Universitaire de Lille
TITRE LONG	Efficacité et tolérance de la neuro-stimulation tibiale postérieure dans la prise en charge des troubles de la vidange vésicale chez les patients atteints d'une sclérose en plaques.
TITRE COURT	Neurostimulation tibiale postérieure et troubles de la vidange vésicale dans la SEP
ACRONYME	NEUROSTIM-SEP1
COORDONNATEUR	Dr Xavier BIARDEAU
CONDITION MEDICALE	Sclérose en plaques
MOTS CLES	Neuro-stimulation tibiale postérieure ; dyssinergie vésico-sphinctérienne ; sclérose en plaques
NOMBRE DE CENTRES	1 centre
RATIONNEL	Neuro-stimulation tibiale postérieure : Autorisation de mise sur le marché dans le traitement de l'hyperactivité vésicale (y compris dans la sclérose en plaques). Efficacité probable de la neurostimulation tibiale dans le cadre de la dyssinergie vésico-sphinctérienne au vu des études récemment publiées dans des populations de patients atteints de sclérose en plaques. Traitement non invasif. Traitement médico-économiquement plus efficient que les auto-sondages propres intermittents.
PLAN EXPERIMENTAL	Il s'agit d'un premier essai pilote monocentrique, prospectif, randomisé, en double, aveugle contre placebo destiné à évaluer l'efficacité de la neuro-stimulation tibiale postérieure comparativement à la neuro-stimulation tibiale postérieure placebo sur l'amélioration de la vidange vésicale Les patients seront attribués aléatoirement dans un des deux groupes : Neuro Stimulation Tibiale Postérieure ($NSTP_{de\ verum}$) vs $NSTP_{placebo}$. Les patients éligibles seront évalués lors d'une première consultation (S-3). Les patients finalement inclus dans l'étude seront évalués lors d'une seconde consultation, avant initiation de la thérapie (S0) A la fin des 12 semaines de traitements, les patients inclus seront de nouveau évalués au cours d'une troisième consultation (S12).
GROUPES COMPARATEURS ET TRAITEMENT(S) ETUDIE(S)	Non applicable
EN CAS D'ESSAI SUR LE MEDICAMENT, PHASE	Non applicable
OBJETCTIFS ET CRITERE(S) D'EVALUATION	**Objectif principal :** **Evaluer l'efficacité de la** neuro-stimulation tibiale postérieure comparativement **à la** neuro-stimulation tibiale postérieure placebo **sur l'amélioration de la vidange vésicale à S12** mesuré par le Bladder Voiding Efficiency (BVE) ratio. **Critère d'évaluation principal :**

	BVE ratio (Bladder Voiding Efficiency) à S12 = Rapport *volume uriné* / *volume vésical total* **Objectif secondaire 1 :** Evaluer l'efficacité de la neuro-stimulation tibiale postérieure à S12 sur les autres paramètres de la vidange vésicale. **Critères d'évaluations secondaires 1 :** - Volume uriné - BUD - Débit urinaire maximal - BUD - Résidu post-mictionnel - BUD - Pression détrusorienne maximale per-mictionnelle - BUD - Volume uriné moyen – Ambulatoire (3 jours) - Débit urinaire maximal moyen – Ambulatoire (3 jours) - Résidu post-mictionnel moyen – Ambulatoire (3 jours) - Fréquence des patients ayant pu arrêter les auto-sondages propres intermittents (RPM < 100 cc) - Questionnaires de symptômes urinaires (USP) - Questionnaires de qualité de vie urinaire (SF-QUALIVEEN) - Questionnaire d'évaluation des auto-sondages (IC-Di-Q) - Atteinte des objectifs (GAS = Goal Attainment Scaling) **Objectifs secondaire 2 :** Evaluer l'efficacité de la neuro-stimulation tibiale postérieure à S12 sur les fonctions ano-rectales et génito-sexuelle. **Critères d'évaluation secondaires 2 :** - Questionnaire de symptômes ano-rectaux (NBD, Wexner) - Questionnaire de symptômes sexuels (MSHQ, FSFI) **Objectif secondaire 3 :** Evaluation des conséquences de la neuro-stimulation tibiale postérieure sur le fonctionnement détrusorien à S12 **Critères d'évaluations secondaires 3 :** - Hyperactivité détrusorienne - BUD - Volume de remplissage lors de la première contraction détrusorienne si HAD - BUD - Pression détrusorienne maximale si HAD - BUD - Capacité cystomanométrique maximale – BUD **Objectif secondaire 4 :** Evaluation de la tolérance de la neuro-stimulation tibiale postérieure à S12 **Critères d'évaluations secondaires 4 :** - Fréquence d'évènements indésirables

POPULATION ETUDIEE	**<u>Critères d'inclusion :</u>** - Patient de plus de 18 ans - Patient de sexe féminin ou masculin - Patient ayant un diagnostic de sclérose en plaques - Patient ayant une dyssinergie vésico-sphinctérienne - Patient pratiquant les auto-sondages propres intermittents comme mode mictionnel exclusif - Patient ayant donné son consentement écrit - Patient assuré social - Patient disposé à se conformer à toutes les procédures de l'étude et à sa durée **<u>Critères de non inclusion :</u>** - Patient présentant une autre pathologie neurologique associée - Patient présentant un score EDSS ≥ 6 - Patient présentant des infections urinaires récidivantes (> 3 épisodes / an) - Patient présentant une hyperactivité vésicale non contrôlée - Patient présentant une hyperactivité détrusorienne non contrôlée - Patient présentant un trouble de la compliance vésicale - Patient ayant bénéficié d'une neuro-stimulation tibiale postérieure dans les 3 derniers mois - Patient porteur d'un boitier de neuro-modulation sacrée - Patient bénéficiant d'injections intra-détrusoriennes de toxine botulinique A itératives - Patient ayant bénéficié d'une injection intra-détrusorienne de toxine botulinique A dans les 9 derniers mois - Patient ayant bénéficié d'un traitement alpha-bloquant dans le dernier mois - Patient présentant une hypertrophie bénigne de prostate (volume prostatique > 40 cc) - Dernière échographie < 6 mois. - Patient présentant un ou plusieurs diverticule(s) vésical (vésicaux) - Dernière échographie < 6 mois. - Patient présentant une dilatation unilatérale ou bilatérale des cavités pyelo-calicielles - Dernière échographie < 6 mois. - Patient présentant un reflux vésico-urétéral unilatéral ou bilatéral – Dernière UCRM < 6 mois - Patient présentant une altération de la fonction rénale (DFG selon CKD-EPI < 60 ml/min/1,73m^2) - Dernier dosage de la créatininémie < 3 mois. - Patient présentant une prothèse métallique au niveau du membre inférieur droit - Patiente enceinte
NOMBRE DE SUJETS NECESSAIRE ET JUSTIFICATION	N= 68 L'objectif principal de l'étude pilote est de fournir des premières données d'efficacité de la neuro-stimulation tibiale postérieure dans la prise en charge des troubles de la vidange vésicale chez les patients atteints d'une sclérose en plaques. Nous proposons de disposer de 30 sujets analysables par groupe pour obtenir des premières estimations pertinentes. En considérant 10% de perdu de vue, 34 patients par groupe seront inclus.
STATEGIE D'ANALYSE STATISTIQUE	Toutes les analyses statistiques seront effectuées de manière indépendante au sein de l'unité de méthodologie, biostatistique et datamanagement du CHRU de Lille. Compte tenu qu'il s'agit d'une étude pilote dont l'objectif est de fournir une première estimation de l'efficacité de la neuro-stimulation tibial postérieur, les analyses seront réalisées chez les cas complets. Pour répondre à l'objectif principal, le BVE ratio à 12 semaines sera comparé entre les deux bras de l'étude par un test t de Student; la différence moyenne (expérimental

	vs. control) avec son intervalle de confiance à 95% sera calculée comme mesure de taille d'effet. En cas d'écart à la normalité, le test U de Mann-Whitney sera utilisé.
PLANNING DE L'ETUDE	Durée prévisionnelle de recrutement : 2 ans Durée de la participation de chaque sujet : 105 jours Durée totale de la recherche : 2 ans et 105 jours
PROCEDURE D'INVESTIGATION SPECIFIQUE A L'ETUDE ET DIFFERENCES PAR RAPPORT A LA PRISE EN CHARGE HABITUELLE	Une bilan urodynamique (BUD) et deux urétro-cystographies rétrogrades et mictionnelles (UCRM) seront réalisées en sus de la prise en charge habituelle. Des débitmétries ambulatoires (2 x 3 jours) seront réalisées en sus de la prise en charge ambulatoire.
EVALUATION DES BENEFICES ET DES RISQUES LIES A LA RECHERCHE	**Bénéfices :** - Reprise de mictions contrôlées en sécurité permettant d'arrêter les auto-sondages propres intermittents. - Ou diminution du nombre d'auto-sondages / jour. - Ou plus grande facilité à réaliser les auto-sondages **Risques :** - Intolérance cutanée des électrodes (urticaire) - Sensations désagréables au niveau du membre inférieur, en rapport avec le courant électrique - Infections urinaires en rapport avec la réalisation des BUD et UCRM.
PARTICIPATION SIMULTANNEE A UNE AUTRE ETUDE	Participation à une autre étude simultanée non autorisée.
PERIODE D'EXCLUSION A L'ISSUE DE LA RECHERCHE	Pas de période d'exclusion prévue à l'issu de la recherche.
JUSTIFICATION DE LA CONSTITUTION OU NON D'UN COMITE DE SURVEILLANCE	Effets indésirables minimes (intolérance cutanée des électrodes, sensations désagréables au niveau du membre inférieur droit, en rapport avec le courant électrique) ne justifiant pas la constitution d'un comité de surveillance.
SOURCE(S) DE FINANCEMENT	Une demande de financement au titre de l'appel à projet *Aide à l'Emergence GIRCI 2018* a été retenue.
NIVEAU DE MATURITE DE LA TECHNOLOGIE DE SANTE TRL	TRL 9

APPENDIX 2: STIMULUS trial - Synopsis

PROMOTEUR	Centre Hospitalier Universitaire de Lille
TITRE LONG	Tibial Nerve STImulation: To Understand its Mechanism of Action on Lower Urinary Tract Disorders in Multiple Sclerosis
TITRE COURT	Tibial Nerve Stimulation and Functional MRI
ACRONYME	STIMULUS
COORDONNATEUR	Dr Xavier BIARDEAU
CONDITION MEDICALE	_
MOTS CLES	Neuro-stimulation tibiale postérieure ; IRM fonctionnelle, Sclérose en plaques ; Hyperactivité vésicale ; Incontinence urinaire
NOMBRE DE CENTRES	1 centre
RATIONNEL	La sclérose en plaques (SEP) est une maladie inflammatoire du système nerveux central. Elle atteint essentiellement les femmes jeunes, avec un âge moyen au diagnostic de 30 ans et un ratio homme : femme de 1:4. Les troubles vésico-sphinctériens sont une des manifestations cliniques les plus fréquentes (>80% des patients), comprenant notamment des troubles de la phase de remplissage associant une hyperactivité vésicale (HAV) – envie urgente et fréquente d'uriner – (26-82%) et/ou une incontinence urinaire par urgenturie (IUU) (27-86%). Il a récemment été rapporté par plusieurs équipes que les patients ayant une HAV/IUU présentaient au cours du remplissage vésical des modifications d'activité des structures cérébrales impliquées dans la régulation du cycle mictionnel (en termes d'activation et de connectivité) ainsi que des modifications dans la régulation du système nerveux autonome. En parallèle, les traitements de l'HAV/IUU, tels que la rééducation pelvi-périnéale, les traitements anticholinergiques, les injections intra-détrusoriennes de toxine botulinique A ou la neuro-modulation sacrée, semblent normaliser – de manière directe ou indirecte - l'activité de ces structures cérébrales, notamment la substance grise péri-aqueducale - considérée comme l'interface principale entre le bras afférent et le bras efférent de la miction. La neuro-stimulation tibiale postérieure (NSTP) est une thérapie de stimulation électrique consistant en l'application d'un courant électrique au niveau de la cheville. Elle est auto-administrée à domicile à raison de 20 minutes par jour. Elle a prouvé son efficacité en deuxième ligne dans le traitement de l'HAV/IUU chez les patients atteints de SEP, avec une amélioration significative des symptômes urinaires à court terme (12 semaines) chez 83,3% à 89% des patients.

	Pourtant, le mode d'action de la NSTP n'a pas encore été clairement étudié. **Nous formulons donc l'hypothèse que la NSTP administrée dans le cadre du traitement de** l'HAV/IUU chez les patients atteints de SEP pourrait normaliser l'activité **et la connectivité des structures cérébrales impliquées dans la régulation du cycle mictionnel ainsi que l'activité du système nerveux autonome.**
PLAN EXPERIMENTAL	Il s'agit d'un essai clinique mono-centrique, non contrôlé, prospectif, réalisée sur un seul groupe de patients visant à mettre en évidence un effet de la NSTP sur l'activité et la connectivité de ces structures cérébrales ainsi que l'activité du système nerveux autonome. Les patientes seront recrutées au cours de consultations de neuro-urologie dédiées à la prise en charge des patients atteints de SEP et présentant des troubles vésico-sphinctériens. Après vérification des critères d'éligibilités et obtention du consentement des patientes, ces dernières seront incluses et initieront un traitement par NSTP pour une durée de 12 semaines consécutives, à raison de 20 minutes par jour. Les patientes incluses seront évaluées avant et 12 semaines après l'initiation du traitement par NSTP, au moyen de : • **Calendrier mictionnel** sur 3 jours • **Questionnaires de symptômes** urinaires (ICIQ-FLUTS, ICIQ-OAB, ICIQ-LUTSqol, QUALIVEEN) • **Bilan urodynamique** associé à un **une mesure de la variabilité de l'intervalle RR** au cours de la cystomanométrie • **IRM cérébrale structurelle et fonctionnelle**, au repos et au cours d'un remplissage vésical continu au moyen d'une colonne d'urodynamique dédiée.
TRAITEMENT(S) ETUDIE(S)	**Urostim2®** (Schwa-Medico, Rouffach, France) Dispositif pour auto-traitement par NSTP **Le dispositif :** Il s'agit d'un stimulateur électrique externe permettant de libérer un courant électrique par voie trans-cutanée à l'aide de deux électrodes adhésives appliquées sur la peau (au niveau de la cheville). **Réglage du dispositif :** Le dispositif permet de délivrer un courant électrique discontinu. Les paramètres, à savoir la fréquence, la durée d'impulsion et l'amplitude peuvent être réglés. Au total, 9 programmes différents sont enregistrés par défaut (U1-U9), et 3 programmes personnalisés peuvent être enregistrés. Le dispositif sera réglé sur le programme U3, validé dans le traitement de l'HAV/IUU (10Hz, 200 mcs), notamment chez les patients présentant une SEP. **Les électrodes :** Les électrodes sont appliquées sur la peau par le patient lui-même, avant chaque séance de stimulation. Elles sont réutilisables pendant 2 semaines consécutives. **Contres-indications :** Présence d'une prothèse métallique au niveau du membre inférieur homolatérale à la stimulation électrique.

	Présence d'un pacemaker **Modalités d'utilisation :** Après apprentissage à l'utilisation du dispositif au cours d'une consultation dédiée, le patient sera autonome pour une utilisation à domicile. Cette utilisation devra être quotidienne, à raison de 20 minutes consécutives / jour.
EN CAS D'ESSAI SUR LE MEDICAMENT, PHASE	Non applicable

OBJETCTIFS ET CRITERE(S) D'EVALUATION	**<u>Objectif principal :</u>** Chez les patientes présentant une HAV/IUU dans un contexte de SEP, évaluer la modification d'activité de la substance grise péri-aqueducale secondaire au traitement par NSTP. **<u>Critère d'évaluation principal :</u>** Variation du niveau d'activation de la substance grise péri-aqueducale à la capacité cysto-manométrique maximale après 12 semaines de traitement par NSTP (différence entre la mesure avant traitement (S0) et la mesure après 12 semaines de traitement (S12). _____ Objectif secondaire 1 : Évaluer la modification d'activité des autres structures cérébrales impliquées dans la régulation du cycle mictionnel secondaire au traitement par NSTP. Objectif secondaire 2 : Évaluer la modification de la connectivité au sein des 3 principaux réseaux cérébraux : DMN « Default Mode Network » (DMN), « Salience Network » (SN) et « Central Executive Network » (CEN) secondaire au traitement par NSTP. Objectif secondaire 3 : Évaluer la modification d'activité du système nerveux autonome secondaire au traitement par NSTP. Objectif secondaire 4 : Comparer la modification d'activité des structures cérébrales impliquées dans la régulation du cycle mictionnel selon l'efficacité clinique de la NSTP. Objectif secondaire 5 : Comparer la modification de la connectivité au sein des 3 principaux réseaux cérébraux : DMN, SN et CEN selon l'efficacité clinique de la NSTP. Objectif secondaire 6 : Comparer la modification d'activité du système nerveux autonome selon l'efficacité clinique de la NSTP.

	_____ Critère de jugement d'évaluation secondaire 1 : Variations des niveaux d'activation des autres structures cérébrales impliquées dans la régulation du cycle mictionnel (cortex cingulaire antérieur, insula, hippocampe, hypothalamus, aire motrice supplémentaire, cortex préfrontal ventro-médial, cortex préfrontal latéral, thalamus) à la capacité cystomanométrique maximale après 12 semaines de traitement par NSTP (différence entre les mesures à S0 et S12) Critère de jugement d'évaluation secondaire 2 : Variations des niveaux de co-variation de l'activité des structures cérébrales impliquées dans chacun des 3 réseaux DMN, SN et CEN au repos après 12 semaines de traitement par NSTP (différence entre les mesures à S0 et S12). Critère de jugement d'évaluation secondaire 3 : Variation de la valeur du « High Frequency Variability Index » (HVFI), obtenu à partir de l'analyse spectrale de la variabilité de la fréquence cardiaque (intervalle RR), à la capacité cystomanométrique maximale après 12 semaines de traitement par NSTP (différence entre les mesures à S0 et S12). Critère de jugement d'évaluation secondaire 4 : Variations des niveaux d'activations des structures cérébrales impliquées dans la régulation du cycle mictionnel à la capacité cystomanométrique maximale (comme décrit au niveau du critère principal et secondaire n°1) et le succès clinique de la NSTP à S12 (défini par une amélioration d'au moins 50% des symptômes urinaires sur le calendrier mictionnel). Critère de jugement d'évaluation secondaire 5 : Variation des niveaux de co-variation de l'activité des structures cérébrales au repos (comme décrit au niveau du critère secondaire n°2) et succès clinique de la NSTP à S12 (défini par une amélioration d'au moins 50% des symptômes urinaires sur le calendrier mictionnel). Critère de jugement d'évaluation secondaire 6 : Variation du « High Frequency Variability Index » (HVFI) (comme décrit au niveau du critère secondaire n°3) et le succès clinique de la NSTP à S12 (défini par une amélioration d'au moins 50% des symptômes urinaires sur le calendrier mictionnel).

POPULATION ETUDIEE	**Critères d'inclusion :** • Age de plus de 18 ans • Sexe féminin • Sclérose en plaques • Trouble de la phase de remplissage à type d'HAV/IUU • Échec, intolérance ou contre-indication à un traitement de première intention de l'HAV/IUU (anticholinergiques) • Consentement écrit • Assuré social • Disposé à se conformer à toutes les procédures de l'étude et à sa durée **Critères de non-inclusion :** • Autre pathologie neurologique associée • Score à l'échelle Expanded Disability Status Scale (EDSS) > 6 (< 3 mois) • Infections urinaires récidivantes (> 3 épisodes / an) • Trouble de la vidange vésicale (RPM > 100ml et/ou plainte fonctionnelle) • Incontinence urinaire à l'effort associée • Traitement anticholinergique dans le dernier mois • Traitement Beta-3 adrénergique dans le dernier mois • Traitement Alpha-bloquant dans le dernier mois • NSTP dans les 3 derniers mois • Boitier de neuro-modulation sacrée en place et activé dans les 3 derniers mois • Injection intra-détrusorienne de toxine botulinique A dans les 9 derniers mois • Prothèse métallique au niveau du membre inférieur • Prothèse métallique non IRM compatible • Pacemaker • Grossesse en cours / Projet de grossesse • Tutelle / curatelle
NOMBRE DE SUJETS NECESSAIRE ET JUSTIFICATION	**NP= 24** L'objectif de l'étude est de mettre en évidence une variation significative (taille d'effet attendu >0.8 en termes de différence standardisée) du niveau d'activation de la substance grise péri-aqueducale à la capacité cystomanométrique maximale après 12 semaines de traitement par NSTP. Pour mettre en évidence cette taille d'effet de 0.8 considérée comme large, avec un test bilatéral (risque alpha= 5%, puissance=90%), et en considérant 20% de patients non-analysables (artefacts de mouvement et perdu de vue), il est nécessaire d'inclure 24 sujets.
STATEGIE D'ANALYSE STATISTIQUE	Les analyses statistiques seront conduites à la l'unité statistique, évaluation économique et data management (SEED) du CHU de Lille. Pour répondre à l'objectif principal, le niveau d'activation de la substance grise péri-aqueducale à la capacité cysto-manométrique maximale mesuré après 12 semaines de traitement par NSTP sera comparé à celui mesuré avant traitement (inclusion) par un test t de Student pour série appariée ou un test des rangs signés de Wilcoxon selon la normalité des différences intra-sujets. L'importance de la

	variation observée sera évaluée par le calcul différence standardisée et de son intervalle de confiance à 95%.
PLANNING DE L'ETUDE	Durée prévisionnelle de recrutement : 12 mois Durée de la participation de chaque sujet : 12 semaines Durée totale de la recherche : 12 mois et 12 semaines
PROCEDURE D'INVESTIGATION SPECIFIQUE A L'ETUDE ET DIFFERENCES PAR RAPPORT A LA PRISE EN CHARGE HABITUELLE	IRM fonctionnelle cérébrale initiale et 12 semaines après l'initiation du traitement par NSTP. • IRM fonctionnelle de repos pour l'étude des connectivités cérébrales. • IRM fonctionnelle d'activation pour l'étude des cartes d'activation cérébrales au cours de la phase de remplissage vésical. Électrocardiogramme pour l'analyse spectrale de la variabilité de la fréquence cardiaque (intervalle RR) au cours de la phase de remplissage vésical.
EVALUATION DES BENEFICES ET DES RISQUES LIES A LA RECHERCHE	**Bénéfices :** Régression des symptômes urinaires à type d'HAV/IUU **Risques :** Intolérance cutanée des électrodes Sensations désagréables au niveau du membre inférieur, en rapport avec le courant électrique
PARTICIPATION SIMULTANNEE A UNE AUTRE ETUDE	Participation à une autre étude interventionnelle simultanée non autorisée.
PERIODE D'EXCLUSION A L'ISSUE DE LA RECHERCHE	Pas de période d'exclusion prévue à l'issu de la recherche.
JUSTIFICATION DE LA CONSTITUTION OU NON D'UN COMITE DE SURVEILLANCE	Effets indésirables minimes (intolérance cutanée des électrodes, sensations désagréables au niveau du membre inférieur droit, en rapport avec le courant électrique) ne justifiant pas la constitution d'un comité de surveillance.
SOURCE(S) DE FINANCEMENT	Une demande de financement sera déposée au titre de l'appel à projets : GIRCI NO « Aide à l'Émergence » 2022.
NIVEAU DE MATURITE DE LA TECHNOLOGIE DE SANTE TRL	TRL 9

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Titre de la Thèse : Optimisation des thérapies de stimulation/modulation électrique dans le traitement des troubles vésico-sphinctériens neurogènes et non neurogènes.

Cadre de classement : Maladies des Appareils Digestif et Urinaire

Mots-clés : Neuromodulation sacrée ; Neurostimulation tibiale ; Système nerveux autonome ; Hyperactivité vésicale ; Incontinence urinaire par urgenturie ; Trouble de la vidange vésicale

RESUMÉ

Même s'il correspond à l'alternance entre une phase de remplissage et une phase de vidange de la vessie, le cycle mictionnel ne peut se résumer à une opération binaire mais implique bien la prise en compte constante de multiples facteurs : le niveau de remplissage du réservoir vésical, la sécurité de l'environnement dans lequel nous vivons, le contexte émotionnel dans lequel nous évoluons et les contraintes sociales auxquelles nous sommes soumis.

On sait aujourd'hui qu'il existe des altérations et/ou des modifications de l'activité et de la connectivité cérébrales, ainsi que des changements dans la régulation du système nerveux autonome (SNA), dans certains types de troubles vésico-sphinctériens - notamment dans l'hyperactivité vésicale ou l'incontinence urinaire par urgenturie et dans certains types de troubles de la vidange vésicale.

Parmi les thérapies disponibles aujourd'hui, les thérapies de modulation/stimulation électrique (neurostimulation tibiale et neuromodulation sacrée) semblent capables de normaliser et/ou de modifier l'activité et la connectivité cérébrales, ainsi que l'équilibre du SNA. Elles pourraient donc apporter, au moins, une réponse partielle à certaines des étiopathogénies sous-jacentes à ces troubles vésico-sphinctériens.

Cependant, le déploiement et le positionnement de ces thérapies de modulation/stimulation électrique sont encore limités par une compréhension incomplète de leurs mécanismes d'action, une identification imparfaite des indications et des populations les plus susceptibles de bénéficier de ces thérapies, un manque de consensus sur le réglage du courant électrique délivré, et un manque d'évaluation à moyen et long terme.

Dans la première partie, nous nous sommes interrogés sur les indications de ces thérapies, et notamment sur leur place dans l'approche préventive des dysfonctionnements vésico-sphinctériens secondaires à une lésion médullaire. Nous nous sommes également interrogés sur la relation, en termes d'efficacité, entre la neurostimulation tibiale transcutanée et la neuromodulation sacrée, afin de mieux soutenir les patients dans le processus de décision médicale partagée. Enfin, nous avons mis au point le premier outil permettant de prédire le succès de la neuromodulation sacrée en tant que traitement du trouble de la vidange vésicale.

Dans la deuxième partie, nous nous sommes interrogés sur les mécanismes d'action, et plus particulièrement sur les changements dans l'équilibre du SNA en réponse à une stimulation aiguë de la racine sacrée.

Dans la troisième partie, nous nous sommes interrogés sur le suivi à moyen terme (5 ans) après l'implantation définitive de la neuromodulation sacrée dans un bassin de population géographique, en recherchant les facteurs de risque d'abandon du suivi.

Ces données, bien que devant encore être complétées par de futurs projets de recherche, nous permettront d'optimiser davantage les thérapies de modulation/stimulation électrique dans la prise en charge des troubles vésico-sphinctériens neurogènes et non neurogènes.

JURY

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