

INUS Neuro-Urology News

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Pediatric Neuro-Urology Working Group

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Pediatric Urologists have been demanding and suggesting greater spaces within institutions for the development of better care of children and adolescents with disorders of the urinary tract and nervous system. This request is based on the need to take advantage of and optimize technological advances and specialized medical knowledge, following the path of our neuro-urologists with adult patients. We believe that INUS represents the institution that can evaluate the needs that we bring and in turn nurture and prepare for the growing influx of adolescent and young adult patients in transition from child to adult care. A large proportion of this subgroup of chronic neuro-urological patients faces a delay in responses at this critical stage and this negatively impacts health.

Each pediatric neuro-urologist member that is part of INUS represents important world-renowned pediatric care centers or is a benchmark in this specialized field. To date, 14 members from America (USA, Panama, Brazil and Argentina), Europe (Italy), Asia (Taiwan) have already joined and we hope that more enthusiastic colleagues will join this great family. The Pediatric Neuro-Urology working group will continue to expand over time, participating in academic activities, research and incorporating other related specialties such as neurophysiology, neurosurgery and physiotherapy. Some topics of interest that we are working on include urodynamics in children with neurogenic bladder, neurogenic bowel and management, neurogenic bladder related to spi-

nal dysraphism, intravesical therapies: Botulinum toxin and anticholinergics, neuromodulation in children, reconstructive surgery for continence and transitional care: bladder augmentation, derivation, bladder neck concerns, sexuality and disability, and others.

Our main interest is to provide our societies and workplaces with greater efficiency in the care of children and adolescents with neurogenic bladder and related entities, as well as to improve the quality of life in this particular population. We believe that this feedback will promote the growth of each of the members and, as a result, strengthen INUS for greater challenges as a society. Pediatric neuro-urologists are grateful to the INUS Board and we want to meet expectations.

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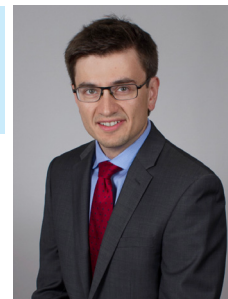
Interview with the Expert

Transcutaneous Electrical Spinal Cord Neuromodulation

Dr. Evgeniy Kreydin  @EKreydin

University of Southern California; Rancho Los Amigos National Rehabilitation Center, **USA**

Glenn Werneburg, MD, PhD, Editor, Neuro-Urology News



Dr. Evgeniy Kreydin is Assistant Professor of clinical urology at the Keck School of Medicine of University of Southern California, USA, and clinical staff at Rancho Los Amigos National Rehabilitation Center. He is the director of genitourinary restoration at the USC Neurorestoration Center. He completed his undergraduate studies at Harvard College and received his Medical Degree at Harvard Medical School. He completed his internship in general surgery and residency in urology at Massachusetts General Hospital in Boston. He then trained as a fellow in female pelvic medicine and reconstructive surgery at University of California, Los Angeles. He is a member of the American Urologic Association, Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction, and the International Neuro-Urology Society. Dr. Kreydin specializes in female pelvic medicine and reconstructive surgery, including the treatment of functional problems of the pelvic floor such as urinary incontinence, overactive bladder, pelvic organ prolapse, urinary fistulas, fecal incontinence and bladder dysfunction due to brain and spinal cord injury. His research focuses on recovery of bladder function after neurological injury, and neurological control of lower urinary tract function.

Together with his colleagues, Dr.

Kreydin recently developed and applied a novel transcutaneous spinal cord neuromodulation (SCONE) technique, in individuals with neurogenic lower urinary tract dysfunction, as well as overactive bladder. In this month's "Interview with the Expert" we discuss Dr. Kreydin's recent work and his career path.

The below is our interview, edited for length and clarity.

Glenn Werneburg: When did you first develop interest in neuro-urology?

Evgeniy Kreydin: As a fellow, I was fascinated with neurologic control of the bladder. I wanted to characterize the neurological pathways that were responsible for the different aspects of storage and voiding. My fellowship was very female urology focused, and there was less neuro-urology involved. Serendipitously, I found the lab of Dr. Reggie Edgerton, who was interested in the restoration of function after spinal cord injury. His main area of interest at the time was the improvement in upper extremity locomotor function after spinal cord injury. In many ways, he was a founder of the field of study of spinal cord stimulation for functional restoration after spinal cord injuries. Many of his former postdoctoral fellows – including Drs.

Susan Harkema and Grégoire Courtine – are now advancing the field.

There was a post-doctoral fellow, Parag Gad, in the Edgerton Lab who was applying epidural stimulation in mice with spinal cord injuries. He found that their lower urinary tract dysfunction improved. Normally, spinal cord injured mice require manual expression of their bladder to void, otherwise they will go into retention and die. But with the epidural stimulation, the mice were able to start voiding again on their own. The group started to explore bladder function in spinal cord stimulation, and I was looking for a research project. They needed a urologist and I needed a basic scientist. The stars aligned and we started working together. Parag has since become my closest collaborator and colleague.

We started this work about 5 years ago, and the lab turned out to be a very supportive research environment, and many patients were enthusiastic about participating. Reggie's original spinal cord stimulation was with epidural stimulation. When I joined, he started exploring transcutaneous stimulation, and that is how the SCONE came to be. We did a couple of pilot studies with 6 to 10 patients where we stimulated patients with spinal cord injuries.

GW: What did you find in these pilot studies?

EK: We found that following SCONE, patients improved their bladder capacity, but also their sensation. We know that improving bladder capacity in those with spinal cord injury can be done with medications or botulinum toxin. But the restoration of sensory function is a different facet of neuromodulation, generally not possible with medication or chemodenervation. I believe that restoration of sensation is the first step of restoration of activity.

GW: How does your clinical work inspire your research efforts?

EK: Clinical work really does inform research in many ways. For example, here at Rancho Los Amigos, I see a very wide variety of patients from able-bodied individuals, to those with stroke, M.S., spinal cord injury, and other neurologic pathology. I had a patient here who had intractable urge incontinence following a stroke. He woke up ten times a night, and was voiding every 15 minutes. Neither medical therapy nor botulinum toxin therapy improved his symptoms. We also tried percutaneous tibial nerve stimulation, which also provided very little benefit. He was desperate, and interested in trying SCONE therapy, which at the time, we had demonstrated was successful in those with spinal cord injury. So, we tried this therapy for him, and it worked remarkably well. He was sleeping more, his urgency and frequency significantly improved. This led us to start looking at this not only for spinal cord injury, but neurogenic bladder in general.

GW: How did you develop a specific interest in stroke?

EK: In SCI, the majority of patients catheterize if they have neurogenic bladder and upper extremity function. As long as these patients are dry between catheterizations, they are often satisfied with this bladder management. But, patients with stroke are very hard to treat. For example, with a man in his 60s with a stroke and an enlarged prostate with severe urgency, the need for self-catheterization following botulinum toxin injection would be a large setback. In a similar individual with spinal cord injury, this is less of a problem as he is likely catheterizing anyway. In addition, medications often are also suboptimal in the stroke population. Thus, neuromodulation is a great option in those with stroke because it has relatively few side effects. In addition, individuals with a history of stroke are a unique and interesting population to study because there is a discrete area in the brain wherein dysfunction leads to lower urinary tract symptoms. The difference between this and Parkinson's, for example, is that here you can look at the stroke location, size, laterality, and severity, and develop models to match the stroke characteristics with the phenotype.

Neuromodulation is different from botulinum toxin injection because it likely addresses a central process within the brain. We know this from sacral nerve stimulation studies from Drs. Howard Goldman and Brad Gill at the Cleveland Clinic, and Drs. Steven Weissbart and Ariana Smith at University of Pennsylvania. Because our other options

lack efficacy or carry significant side effects, such as catheterization, I believe neuromodulation is a great solution for this population.

GW: Please describe your recent studies using SCONE in those with stroke and other neurourological conditions.

EK: In 2020, we published a study wherein we used SCONE technology on individuals with stroke and multiple sclerosis. Following SCONE, we looked specifically at bladder overactivity and detrusor overactivity, and we showed that these patients had increased bladder capacity, improved sensation, and improved gradual sensation. Concurrently, I started thinking about whether we could do with SCONE and stroke what the investigators at Cleveland Clinic did with OAB patients, and Dr. Rose Khavari did with the transcranial neuromodulation technique she developed for M.S. patients. So, we started recruiting for a study wherein patients with stroke underwent SCONE stimulation – and had functional MRI scans before and after they underwent stimulation. Because our setup allows us to perform urodynamics and have patients void inside the scanner, we are able to detect when their detrusor overactivity occurs, and correlate that event with specific activity detected on their fMRI. This study was funded by the Urology Care Foundation through the American Urological Association.

Our results thus far have been very interesting. When we did our initial study, we compared healthy control volunteers to those who had a stroke and developed LUTS. We found that patients with stroke exhibited significantly reduced cortical activity compared to healthy controls. In this study, patients that underwent stimulation experience an improvement in their lower urinary tract symptoms. Interestingly, the improvement that we see is sensory. We also see improvement in bladder capacity and continence, but importantly, patients report that they feel their bladder better. They now report a gradual rise in sensation and urgency, rather than the “zero-to-sixty” sensation seen during a detrusor overactivity contraction.

On imaging, we found increased activation of the cortex following SCONE neuromodulation compared to before stimulation. This is in line with our initial study, which demonstrated that patients with stroke experienced significantly decreased activation of the cortex compared to healthy controls. The results also were in line with other studies such as that of Rose Khavari, showing that those with more severe voiding dysfunction with MS have decreased cortical activity. The cortex is not critical to urination, but it appears that it is very important for regulating the sensation of urgency and regulating when micturition occurs, and switching from storage to voiding. These results gave us insight into the potential mechanism of SCONE in this population, and how it relates to other neuromodulation techniques reported in previous studies.

GW: What are your next steps?

EK: The weakness of our studies all along – including in our fMRI study – is that we did not have a placebo arm. Placebo in neuromodulation is very important, given the known large placebo effect in this treatment and population. We are now doing a randomized, controlled, trial of SCONE. We are recruiting patients in several centers across the country to undergo SCONE therapy for overall improvement for neurogenic bladder. We ultimately hope to perform fMRI scans in such a study to determine how these brain activity changes are impacted by sham versus neurostimulation.

GW: What advice do you have for junior members of INUS who are looking to embark on a career as clinician-investigators in neuro-urology?

EK: Be open-minded to both the direction in which your life is taking you, as well as the ideas other people have. For example, I’ve always been interested in Neuro-Urology. I’ve been interested in function, and how that leads to pathology. I had very minimal exposure to female urology in my residency, and I did not have a particular interest in the subspecialty. But winding up at UCLA, a female-focused fellowship, was one of the best things that ever happened to me. I learned this new discipline, which I now find very interesting. I know how to take care of female patients with urological issues. I was very fortunate to find this discipline, wherein there is ever-increasing need. Fifty percent of the population is female, and there is increasing life expectancy, and

female urological problems are becoming more and more prevalent. Expanding one’s clinical expertise will only make one a better scientist, clinician, and surgeon. Many clinician-scientists know what we are passionate about early on. It is easy to lose track of the world outside of it. Staying broad-based in one’s interests, being aware of the important underlying mechanisms and needs, and understanding patterns in one’s clinical practice are all important and integral to being a good scientist. It gives you a unique perspective that most non-clinicians don’t have.

Further Reading

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Meet the Board Member

Stefania Musco, MD

[@drmusco](#)

Consultant Urologist in Neuro-Urology, Careggi University Hospital, Florence, **Italy**
INUS Secretary

Dr. Stefania Musco, MD, is the new secretary of the INUS Board. Since 2016 she has been working as a consultant urologist in Neuro-Urology at Careggi University Hospital, Florence (IT). She moved from her beloved native Sicily in 1995 and left her conservatory studies midway to start studying medicine in Rome at Campus Biomedico University, but she brought her piano with her to keep on playing classical music in her free time. During her studies she got excited about pursuing urology thanks to her first mentor, Professor Michele Gallucci. Afterwards, during her residency as a urologist in training in which she also got a one year honorary contract at the Prostate Unit of Charing Cross Hospital in London (Dr. Simon Carter), she had the great opportunity to work under Enrico Finazzi Agrò who helped her make her first real choice in medicine: Neuro-Urology. Thanks to him, she networked with one of the most well-known figures nationally and internationally in Neuro-Urology, Dr. Giulio Del Popolo who fulfilled her dream, allowing her to grow professionally and scientifically, and improve her personal knowledge and surgical skills in this field. After about two transitional years during which she commuted from Rome to Florence

every 3 days so as not to lose touch with friends and for other personal reasons, she finally decided to begin a new chapter and moved to Florence in 2014. Prior to that, following a one-year preparation course as a volunteer, she travelled for about a month around Senegal to train young local student doctors and nurses on health screenings for children. From that powerful, deep experience looking at the African night skies, she has always kept in mind what solidarity and cooperation really means.

The following year she had the opportunity to be involved as associate panelist in elaborating the EAU Neuro-Urology guidelines where she's still an active member.

In 2017, she had the great honor of being the local committee organizer in charge of the unforgettable and hugely successful ICS international annual meeting which was held in Florence. Since 2018 she has been a trustee board member of the Italian Urodynamic Society (SIUD) and for the last 2 years she has had a joint appointment as SIUD Secretary. She is also an active member of the Italian Urology Society (SIU) and recently involved in the SIU female urology working group. She has been acting as a reviewer for several

indexed medical journals such as Neurourology and Urodynamics, International Brazilian Journal of Urology, European Urology, British Journal of Urology, BMC Urology, Urologia internationalis, and Asian Journal of Urology. She has almost 40 publications on Scopus and more than 500 citations.

Her main areas of interest are Neuro-Urology, urodynamics, diagnosis and treatment of female and male urinary incontinence (pelvic floor rehabilitation, intravesical treatments, midurethral sling procedures, artificial sphincter, neuromodulation techniques including tibial, sacral and pudendal).

She has been involved in several multicenter randomized trials, and her current research includes interneural and conditional closed-loop peripheral nerve stimulations, quality of life in neuro-urological patients and surgical options for neurogenic stress and mixed urinary incontinence.

In her spare time, she still plays piano, climbs with her partner and plans her next journey!



Literature Review

Ana Vidal Brandt, MD

Urology Specialist and Fellow, Urologists of Mexico, Mexico City, **Mexico**

Sacral Neuromodulation for Neurogenic Lower Urinary Tract Dysfunction.

Liechti, M. D., van der Lely, S., Knüpfer, S. C., Abt, D., Kiss, B., Leitner, L., ... & Kessler. *NEJM Evidence*, 2022.

There is a lack of randomized controlled trials (RCTs) assessing the efficacy of sacral neuromodulation (SNM) for neurogenic lower urinary tract dysfunction (NLUTD). In this sham-controlled, double-blind, multicenter clinical trial with two parallel groups, the authors assessed the efficacy and safety of SNM in NLUTD using the same approach to for non-NLUTD: a test phase, followed by an optimization phase, and then a blinded intervention phase to determine whether the benefits observed in the test phase were sustained or reversed in the 2-month trial phase during which patients were unaware of their neurostimulator “on” versus “off” status.

The success of SNM was defined as improvement of at least 50% in the bladder diary variables for the urgency group or a greater than or equal to 50% decrease in the postvoid residual in the retention group; and both in the combined group.

A total of 124 patients with symptomatic refractory NLUTD were included and underwent minimally invasive lead placement (Medtronic, Inc., Minneapolis, MN, USA) into the sacral foramina S3 and/or S4. Of these patients, 65 (52%) had a successful SNM test phase and a permanent neurostimulator was implanted. Following a positive SNM test and optimization phase, 60 participants were randomly assigned to a 2-month double-blind SNM ON (29)

or SNM OFF (31) treatment.

In the blinded intervention phase, patients in the SNM ON group were more likely to show sustained beneficial SNM effects (success: 22 of 29 [76%]), compared with the patients of the SNM OFF group, who tended to deteriorate compared with their test phase values (success: 13 of 31 [42%]).

The authors concluded that SNM was effective and without device-related side effects once the testing and optimization phases were complete in the group of highly selected neurologic patients. The randomized study design not only proved SNM-specific treatment effects, but also the need for continuous SNM.

Assessment and Treatment of Nocturia in Neurological Disease in a Primary Care Setting: Systematic Review and Nominal Group Technique Consensus

van Merode, N. A., Dawson, S., Coulthard, E., Henderson, E. J., Rice, C. M., Rees, J., ... & Drake, M. J. *European Urology Focus*, 2022.

Nocturia in neurological disease is an under-researched area, and its initial management is generally undertaken in primary care. This study aimed to rationalize the initial management of nocturia for particular use in nonspecialist settings. Thirteen studies were included, and all the participants were recruited through secondary care.

The use of extended-release levodopa in patients with Parkinson’s disease (PD) showed a reduction in nocturia episodes following two months of treatment. A significant reduction in the number of nocturia episodes per night

was found with oxybutynin in patients with PD, Multiple Sclerosis (MS), and Spinal Cord Injury (SCI). Mirabegron significantly reduced the mean number of nocturia episodes per night in patients with PD. The effect of OAB drugs in reducing the severity of nocturia can be expected if the nocturia is driven by urgency. In patients with MS, pelvic floor muscle training (PFMT) and percutaneous tibial nerve stimulation (PTNS) reduced the number of nocturia episodes.

The varied etiology of neurological disease is likely to have implications for reducing nocturia episodes, and is a key factor for improving outcomes. For individuals with neurological disease, nocturia may reflect a neurologically-driven cause, or a cause unrelated to neurologic pathology, typical in older populations. The evaluation in primary care should include potential mechanisms, including comorbid causes, and environmental factors that could affect the condition or its treatment. These are intended to direct therapy according to the underlying mechanism, and to facilitate a response.

Another important aspect in neurological disease is the identification of enuresis and nocturnal polyuria, which is why more widespread use of bladder diaries is needed; these may need practical adaptations to make their use for a disabled population easier in primary care.

This systematic review underscores the lack of information about nocturia, especially in patients with neurological diseases and that more control trials are needed.

INUS Calendar

INUS Lectures at the 2nd Meeting of the Mexican Society for Urogenital Sciences
Tlaxcala, Mexico
September 28-October 1, 2022

INUS lecture at the EUCS-PACS 2022 (11th Emirates Urological Conference and 18th Pan Arab Continence Society Conference)
Dubai, United Arab Emirates
October 28-30, 2022

42nd Congress of the Société Internationale d'Urologie
Montreal, Canada
November 9-13, 2022

INUS seminar on Neuro-Urology in Practice. Focus on diagnostic workup and urodynamics.
Bratislava, Slovakia
December 3, 2022

INUS Annual Congress 2023
Athens, Greece
June 8-10, 2023



INUS Annual Congress Athens, Greece June 8-10, 2023



Join the International Urology Community in Montreal
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Palais des congrès de Montréal

Save the date!
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