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The Challenge of Overactive Bladder Therapy: Alternative to Antimuscarinic Agents

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ABSTRACT

Contemporary, the management of overactive bladder (OAB), a medical condition characterized by urgency, with or without urge urinary incontinence, frequency and nocturia, in absence of genitourinary pathologies or metabolic factors that could explain these symptoms, is complex, and a wide range of conservative treatments has been offered, including bladder training, biofeedback, behavioral changes, oral or intravesical anticholinergic agents, S3 sacral neuromodulation and peripheral electrical stimulation. Clinical efficacy of these treatments remains an open issue and several experimental and clinical studies were carried out in the last years improving the results of medical treatment.
Here we review the pathophysiology of micturition reflex, the current therapies for OAB and the rationale for alternative treatments. Furthermore we critically address the potential use of medications targeting the central nervous system (CNS) and the primary sensory nerves of the bladder wall, we review the use of agonists of nociceptin/orphanin protein (NOP) receptor and finally we report the results obtained by intradetrusor injection of botulinum toxin.

***Key words**: overactive bladder; voiding dysfunction; pharmacotherapy; receptor, orphanin fq; botulinum toxins*
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INTRODUCTION

Overactive bladder (OAB) is a medical condition characterized by urgency, with or without urge urinary incontinence, frequency and nocturia, in absence of genitourinary pathologies or metabolic factors that could explain these symptoms (1). This definition represents an important clinical message because in the era of High-Tech medicine, people look for medical help in the same way as in the past as a result of symptoms. The key symptom, which characterizes OAB, is "urgency": the sudden and compelling desire to pass urine, which is difficult to defer.

OAB affects one sixth of European population aged 40 years or over (2) and similar data have been reported also for United State of America where around one sixth of adults aged 18 years and over have symptoms of OAB; the estimated prevalence is 33 million US residents aged over 18 years (3). Recently Erwin reported a cross-sectional population-based survey of people > 18 years showing that the total prevalence in 4 European countries is 12.2% and confirmed that OAB is a common condition in men and women across all adult age group (4). One third of people with overactive bladder have urge urinary incontinence and large population studies have reported that the prevalence of symptoms of OAB increases with age (5).

The aim of this paper is to address critically the therapy of OAB providing an up-to-dated insight on alternative strategies to antimuscarinics.

PATHOPHYSIOLOGY OF MICTURITION REFLEX

The lower urinary tract serves two main functions: the storage of urine without leakage (storage phase) and the periodic release of urine (voiding phase). During the storage phase the detrusor muscle is relaxed and the outlet region is contracted to maintain continence. During the voiding phase the detrusor muscle contracts and the outlet region relaxes facilitating bladder emptying. These two functions are dependent on central, peripheral autonomic and somatic neuronal pathways and local peripheral factors. During the storage phase the afferent impulses reach the central nervous system (CNS) from the lower urinary tract and afferent activity sends information to the periaqueductal grey of pons. In the pontine tegmentum there are two regions: a medially located one (M-region), which corresponds to Barrington's nucleus or pontine micturition center which is responsible of coordination of micturition reflex (6), and a laterally located one (L-region), which is involved in the storage phase suppressing the bladder contraction and improving external sphincter muscle activity during this phase (7). The emerging development of functional imaging such as single photon emission tomography (SPET), positron emission tomography (PET) and functional MRI showed several sovraspinal-sovrapontine (cortical) areas involved in the micturition reflex, but so far their specific role remains obscure (8-10).

Three different sets of peripheral neuronal systems are involved in the micturition reflex: the parasympathetic system the sympathetic system and the somatic system. The parasympathetic system originates in the sacral level of the spinal cord (S_2-S_4) and provides an excitatory input to the bladder by the postganglionic nerve terminal release of Acetylcholine (Ach), which excites muscarinic receptors (M_2, M_3) in the detrusor smooth muscle leading to the bladder contraction. The sympathetic system originates in the thoracolumbar cord (Th_{11}-L_2) and provides an inhibitory input to the bladder by the postganglionic nerve terminal release of norepinephrine (NA) which excites β_3 receptors in the body of the detrusor leading to the bladder relaxation. The sympathetic system also provides an excitatory input to the urethra smooth muscle by the postganglionic nerve terminal release of norepinephrine (NA) which excites α_1 receptors in the urethra leading to the urethral closure. The somatic system provides an excitatory input to the striated urethral muscle; in this case the motoneurons are located along the lateral border of the ventral horn of the sacral spinal cord, which is known as the Onuf's nucleus. They release Ach, which acts on nicotinic receptors to induce muscle contraction.

Immunohistochemical and morphological studies, which have been conducted on the bladder wall, showed that there are a lot of neuronal terminal endings that do not correspond to cholinergic and adrenergic innervations (11). These nerves, which are non adrenergic - non cholinergic (NANC), are peptide containing fibers and they are selectively sensitive to capsaicin, the pungent ingredient of red peppers, heat and H^+. They are primary afferents and may play an important role in the regulation of lower urinary tract functions (12). These nerves consist of small myelinated Aδ and un-myelinated C fibers, which are, however, "silent" under normal conditions.

Data from several laboratories have recently shown the importance of peripheral local factors in the regulation of micturition reflex. The bladder urothelium can respond to chemical and mechanical stimuli releasing different mediators, which target the receptors of adjacent sensory nerves (13). Birder introduced the concept of "neuron-like properties" of urothelium. Urothelium responds to stretch, during the filling phase of micturition reflex, by increasing the size of apical umbrella cells and by releasing mediators, which activate sensory fibers (14). Finally several investigators suggest a regulatory role for interstitial cells, which are part of a "vesical module" consisting of nerves, smooth muscle cells and interstitial cells. It is thought that this module may receive diverse inputs and may be able to modulate local reflex or activity (15).

OAB may result from increased bladder afferent activity, decreased capacity to handle afferent information or decreased suprapontine inhibition in the CNS, and increased peripheral sensibility to release mediating transmitters. This last situation,

known as "bladder oversensitivity", could originate from the release of neurotransmitters by urothelium or sensitization of sensory nerves by paracrine pathways. The CNS as well as the periphery may represent the target for a new class of medications against OAB.

CURRENT THERAPIES FOR OVERACTIVE BLADDER

Anticholinergics, which antagonist Ach for the muscarinic receptors, are first line pharmacological treatment for overactive bladder. The indication for the treatment of OAB derives from a high level of evidence (Level-1) and high grade of recommendation (Grade-1) (16). Anticholinergics produce significant symptom improvements in OAB syndromes when they are compared to a placebo and the number of anticholinergic drugs available on the market is increasing. However, the debate about the pathophysiological rationale and the clinical use of antimuscarinic agents remains an unsolved issue.

Herbison reported a systematic review of anticholinergic drug treatment compared to a placebo therapy in the treatment of overactive bladder as a result from randomized controlled trials (17). He found that those patients receiving active treatment were more likely to be subjectively improved and they had about one leakage episode less in 48 hours than those taking placebo. Urodynamic assessment showed larger increase in maximum cystometric capacity in those receiving active treatment and the volume at first contraction increased more in the drug group than in the placebo group. Dry mouth was the most frequently reported side effect. Herbison concluded that although statistically significant, the differences between anticholinergic drugs and placebo were small, apart from the increased rate of dry mouth in patients receiving active treatment. For many of the outcomes studied, the observed difference between anticholinergics and placebo may be of questionable clinical significance.

After the publication of this paper many urologists felt that Herbison had inappropriately written off this class of drugs and that the author had a preconceived notion about anticholinergics. Chapple et al. carried out a systematic review and a meta-analysis on the effects of antimuscarinic in the OAB therapy (18). His review was planned to assess the safety, tolerability and efficacy of antimuscarinic in the OAB therapy, considering the effects on quality of life (QoL), differences between different antimuscarinics and, finally, addressing criticism of Herbison's review. Chapple's review has many differences regarding Herbison's study. He did a systematic analysis of QoL data, a differentiation between individual antimuscarinics, including active controlled trials and following a "splitting" approach and not a "cumulative" approach. Chapple et al. reported that antimuscarinic formulations, apart from Oxybutynin IR (immediate release) were found well tolerated and no drug was associated with a significant risk of death. Also, in this review dry mouth was the most commonly reported adverse effect, even if other adverse reactions were included (blurred vision, constipation, dyspepsia, nausea, vomiting, urinary retention). Antimuscarinics were able to reduce frequency, urgency episodes by over one episode per day, incontinence by half an episode or more per day and the volume voided per micturition was increased. Finally patients receiving antimuscarinics have greater improvements in QoL than patients on placebo arm. Chapple et al. (18) concluded that there is a quantifiable objective and clinical benefit conferred by antimuscarinics in the therapy of OAB.

However, most of the studies, which were considered in the review, had limitations of evidences such as choice of outcome measure, trial length, restricted population, the high placebo effect and economic issues. For all these reasons, today, many of us are disputing formally and systematically in order to trigger an appropriate response to the question on the rational of use of anticholinergics and for finding alternative therapies.

RATIONALE FOR ALTERNATIVE THERAPIES TO ANTICHOLINERGICS

In the past, many factors discouraged the extensive research on new drugs in the treatment of OAB

or LUTS. The main limitations were due to the complex neuropharmacological arrangement of voiding reflex and sexual function, the simple "easy to accept" idea of antagonistic, parasympathetic cholinergic and sympathetic adrenergic control of the LUT and the complex interrelationship between the voluntary somatic control of visceral reflex and the involuntary components.

In the last 2 decades the neuropharmacology gained advantages from basic science research and the experimental results were translated in the clinical practice. The main advantages were due to the discovery of non-adrenergic - non-cholinergic innervation (NANC) of the LUT (19), the recognition of a multiplicity of neurotransmitters (monoamines, purines, amino acid, peptides and nitric oxide) (11), the concept of co-transmission (nerves release more than one transmitter) and the recognition of the basilar importance of a sub set of sensory nerves which are sensible to capsaicin, the pungent ingredient of red chilli, in the control of micturition reflex (20). Finally, the discovery of a new variety of different receptors, involved in the regulation of sensory nerves' conduction and changes occurring during not only development and ageing but also after trauma or chronic inflammation (neuroplasticity), were basilar for the development of alternative therapies (21-23).

Today CNS, sensory nerves and bladder smooth muscle cells represents the main targets of alternative strategy for OAB.

CENTRAL NERVOUS SYSTEM

Several CNS transmitters/receptors systems, including adrenoceptors, γ-aminobutyric acid (GABA), opioid, serotonin, noradrenaline, dopamine, and glutamatergic receptors are known to be involved in micturition control (24).

Several and different adrenoceptors have been found in the brain and spinal cord. High levels of α_{1A} mRNA have been showed in many hypothalamic nuclei, α_{1A} mRNA and α_{1B} mRNA in amygdala and raphe nuclei and α_{1D} mRNA in the cortex, hippocampus and amygdala. Different studies showed that i.t. or i.c.v. α_1 antagonists reduced the detrusor overactivity in the spontaneously hypertensive rat, i.t. or i.c.v. tamsulosine inhibits the micturition reflex by the activation of spinal receptors and α_2 agonists produce the activation of micturition reflex by the activation of supraspinal and spinal receptors (25). α_{1A}-, α_{1B}-, and α_{1D}-AR mRNA can be demonstrated in the parasympathetic nucleus in the sacral spinal cord (26) and α_{1d}-AR KO mice vs. wild type controls showed lower voiding frequency, larger bladder capacity and larger voided volumes (27). Naftopidil and tamsulosin both block α-ARs in prostatic smooth muscle, and both agents (especially naftopidil) may also act on the lumbosacral cord (28). It is interesting report that tamsulosin and aftopidil in a 8-week crossover-study on 96 BPH patients decreased the I-PSS for storage symptoms (29). This study suggests that naftopidil is as effective and safe as tamsulosin and both drugs were effective in improving storage and voiding symptoms. However, there was no difference in clinical efficacy or adverse effects between the α_1 AR antagonists with different affinity to α_1 subtypes, α_{1A} and α_{1D} (30).

There has been little interest in developing drugs active on opioid mechanisms for the treatment of bladder disorders, despite the profound inhibitory effects that morphine and analogs have on the micturition reflex. However, tramadol, which is both a μ-receptor agonist and an inhibitor of noradrenaline and serotonin uptake, has been reported to have promising effects on micturition in animal models (31). Tramadol produced the inhibition of detrusor overactivity induced by cerebral infarction in rats and the inhibition of detrusor overactivity induced by apomorphine in rats (32).

Serotonin and its receptors may play an important role in the central regulation of micturition reflex. Exposure to selective serotonin reuptake inhibitors (SSRIs) is associated with an increased risk (15/1000 patients) for developing urinary incontinence especially between the elderly and users of sertraline are at the highest risk (33). Clomipramine treated female rat pups void more frequently than controls, have a lower bladder capacity and show detrusor overactivity. Fluoxetine treatment reverses these effects. Up to date, no convincing documenta-

tion exists whether or not SSRIs are effective in the treatment of OAB, and despite positive acute effects in preclinical models, there are no proof of concept studies showing that subtype selective 5-HT receptor antagonists (5-HT1A, 5-HT7) are effective in the OAB treatment.

In the normal rat, stimulation of GABA receptors, mainly in the central nervous system, inhibits micturition. Antagonism of $GABA_B$ receptors stimulates micturition, suggesting that the receptors are under tonic GABAergic influence. Intrathecally baclofen attenuates oxyhemoglobin induced detrusor overactivity, suggesting that the inhibitory actions of $GABA_B$ receptor agonists in the spinal cord may be useful for controlling micturition disorders caused by C-fiber activation in the urothelium and/or suburothelium (34). Recently experimental studies have demonstrated the inhibitory effect of exogenous gamma-aminobutyric acid (GABA) on micturition. Tigabine inhibits the micturition reflex in rat and its site of action, which may be central (35).

Finally, Kim reported the effects of gabapentin in 14 out of 31 patients with refractory OAB. He found an improvement of clinical parameters with fewer side effects, gabapentin was generally well tolerated, and it can be considered in selected patients an alternative treatment to antimuscarinics.

In conclusion, several promising new principles have been recently investigated, but only few drugs have passed the stage of "proof" of concept.

SENSORY NERVES

Recently, the idea of afferent blockade by targeting afferent nerves that control the micturition reflex has gained the trust of urologists as a potential alternative to current drug therapies. The emerging concept is that it would be more desirable to prevent the micturition reflex that initiates overactive bladder, instead of blocking the contraction of detrusor smooth muscle. The concept of a therapeutic approach through the modulation of the afferent arm of the micturition reflex emerged when investigators studied the effect of capsaicin on sensory nerves. Capsaicin targets the transient receptor potential vanilloid-1 (TRPV1), which is expressed on small-to-medium size afferent neurons, which are most of C-type but also in a fraction of A-δ type. The acute exposure to capsaicin depolarizes and excites sensory fibers expressing TRPV1 receptors. This excitation is followed by a refractory period. It means that the repeated, long-term, high dose exposure to capsaicin desensitizes, defunctionalizes and ultimately damages peripheral terminals, which become unresponsive. In other words, the mechanism of action by which capsaicin works is a long lasting reversible suppression of sensory nerve activity and it is dependent on dose, time of exposure and interval between consecutive instillations.

The proof of concept that an inhibitory modulation of urinary bladder afferent nerves could achieve a therapeutic benefit in the treatment of bladder overactivity, was obtained through the intravesical instillation of repeated low concentration doses or single high concentration doses of capsaicin (20). The first experiences were performed in patients with neurogenic detrusor overactivity. De Ridder reported that repeated instillations of intravesical capsaicin was effective in approximately 80% of the patients with bladder overactivity due to spinal cord disease and the beneficial effect lasted 3 to 5 years (36). At the end of the 1990s Lazzeri questioned the efficacy and the safety of capsaicin for the management of detrusor hyperreflexia (37) and Petersen demonstrated, in a placebo controlled crossover study, that intravesical treatment with capsaicin did not show beneficial effects on detrusor hyperreflexia and produced significant reactive changes in the bladder mucosa (38). Lazzeri reported that 12.96% of patients had a significant episode of autonomic dysreflexia during the infusion, 35.18% presented rhythmic detrusor contractions causing the leakage of urine and 96% of the patients with incomplete spinal lesion and bladder sensation reported a warm/burning/painful sensation (39). de Seze, by Bordeaux group, found that the capsaicin side effects were due to alcohol (the vehicle), which were used, sometimes, at the concentration of 30%. When capsaicin was diluted in glucidic acid, intravesical instillation was equally effective with fewer adverse events (40). Owing to the warm/burn-

ing sensation/discomfort that capsaicin produced in subjects with normal sensation and increasing the regulation of non licensed agents, the source of capsaicin mostly having been chemical rather than pharmacological suppliers, was replaced by the pharmaceutically prepared resiniferatoxin (RTX). RTX, obtained from a cactus species of the genus Euphorbia, Euphorbia resinifera, is an ultra potent capsaicin analogue to a thousand fold the selective C-fiber neurotoxicity of capsaicin for comparable pungency and with fewer side effects. Against a strong scientific background of its demonstrated mode of action in animal models, the use of this agent therefore held out the promise of an effective "de-afferenting" instillation with little discomfort. However , the reality to date has unfortunately been otherwise. Following early positive reports of its effectiveness in both neurogenic (41,42) and idiopathic detrusor overactivity (43) large scale placebo controlled multicentric clinical trials in Europe and the US were initiated to examine the efficacy of the agent in patients with neurogenic bladder. During the course of these studies it became apparent, to those involved in the trials, that many patients were not responding at all, which lead to a review of the study procedures and the recognition of the possible loss of active drug availability due to the adsorptive properties of RTX to plastic. Immunohistochemical evidence showed that responders had a demonstrable reduction of nerve density of suburothelial innervations, with a parallel reduction in the expression of TRPV1 and P2X receptors (44,45) of these nerves.

Other centers continued to examine the efficacy of RTX in detrusor overactivity (46,47) and because of the known effect of RTX on afferent innervations, a study looked at its efficacy in conditions of bladder pain or interstitial cystitis (48). Encouraged by positive finings, a pharmaceutical company recently funded a large scale placebo controlled study using RTX to treat interstitial cystitis. Unfortunately the reported benefits were no greater in the active treatment than the placebo group and it therefore seems unlikely that a pharmaceutical preparation of RTX will continue to be made available unless there is some further development in this field.

Recently experimental and clinical evidence has showed that the inhibitory system nociceptin/orphanin (NO) FQ - nociceptin/orphanin protein (NOP) receptor, may play an important role in the modulation of micturition reflex. Nociceptin inhibits the activity of TRPV1-expressing neurons at the peripheral level by the activation of a specific G-protein coupled receptor named nociceptin orphan peptide (NOP) receptor (49). In a pilot, uncontrolled study, the intravesical infusion of N/OFQ increased the bladder capacity in a selected group of patients suffering from neurogenic detrusor overactivity, but not in normal subjects (50). These findings were replicated in a placebo-controlled randomized study suggesting that NOP receptor agonists modulate the micturition reflex in humans and they could represent a suitable alternative to the treatment of OAB to oral antimuscarinics (51).

BOTULINUM TOXIN

Botulinum toxin (BTX) is a complex protein, produced by the anaerobic bacterium Clostridium botulinum. Previously known only as a cause of a serious and often fatal paralysis acquired through ingestion of contaminated food, the neuromuscular blocking effect of the toxin has been thought that might alleviate muscle spasm due to excessive neural activity of central origin. Local injections of BTX have been showed effective in the treatment of strabismus, essential blepharospasm, and hemifacial spasm and further studies indicate that BTX injections also can provide useful symptomatic relief in a variety of other conditions characterized by involuntary spasms of certain muscle groups, notably in focal or segmental dystonia including spasmodic torticollis, oromandibular dystonia (orofacial dyskinesia, Meige syndrome), and spasmodic dysphonia. Recently the unlicensed use of toxin in the treatment of lower urinary tract (LUT) conditions has been described. (52). LUT disorders are characterized by detrusor sphincter dyssynergia (53,54), detrusor overactivity neurogenic detrusor overactivity (NDO) (55) and also idiopathic detrusor overactivity (IDO).

Botulinum toxin is thought to work by cleaving a synaptosome-associated protein, SNAP-25, thereby blocking the presynaptic release of acetylcholine at the neuromuscular junction. This protein is part of SNARE complex, which is vital for vesicular exocytosis and relies of Ach. It is important to remind that, after exposure to botulinum toxin, neuronal death does not occur, but the phenomenon of re-sprouting of axons, leading to new synaptic contacts, also occurs and these presumably account for the return to muscular function, which is observed after a number of months (56). The re-sprouting of axons might also play a role in hyperactivity of muscular function or reduction of compliance in case of the bladder injection repetition.

In the last year several investigators suggested that BTX might affect urothelium/ suburothelium sensory innervations. BTX-A has been found to reduce pathologically elevated levels of neurotransmitters including ATP, to decrease the number of suburothelial afferent neurons expressing purinergic receptors and to reduce urgency (57,58). The exact mechanism of action on the afferent pathway remains unknown.

Following the remarkable efficacy seen in studies with NDO, a number of researchers have investigated BTX use in patients suffering from antimuscarinic refractory IDO. Chancellor was the first to investigate the effect of BOT in a group of patients with overactive bladder refractory to other conservative treatments (59). Rapp investigated the effects of injection of botulinum toxin in thirty-five patients (29 women and 6 men) with frequency, urgency, and/or urge incontinence (60). The patients received 300 UI of BTX-A injected transurethrally at 30 sites within the bladder. Overall, 21 (60%) of 35 patients reported slight to complete improvement of voiding symptoms after 3 weeks. Among the initial responders followed up for 6 months an improvement of quality of life was reported in most patients with fewer side effects. Due to the increased understanding of the role of the urothelium in OAB, Kuo assessed sub-urothelial injections of BTX (61). It was found that although this method of administration was more effective than detrusor injections, there was impaired bladder sensation and voiding efficiency. Voiding difficulty was reported by 75% of patients, and 30% required catheterization. This suggests that blockade of detrusor contractility through sub-urothelial sensory fibers was much more pronounced than at neuromuscular junctions or that only a small amount of diffusion of BTX from the detrusor to the sub-urothelium occurs following detrusor injection. More recently Schulte-Baukloh performed BTX injections in patients with refractory OAB symptoms but with no evidence of DO on prior urodynamics (62). Significant improvements were seen in symptoms scores, bladder diary and urodynamic parameters. In this group of patients no increased PVR or need for CISC was noted even with a dose of 300 UI of BTX. In order to avoid acute urinary retention or PVR, all patients had 50-75 UI of the BTX concurrently injected into the external sphincter without increasing stress incontinence rate.

Several studies supported the BTX as promising therapy in urological disease conditions as previously described, however additional investigations, including controlled clinical trials, are needed. Further studies of the mechanism of action of botulinum toxin and its pharmacotherapeutics are also needed and international standardization of measures of biological activity of botulinum toxin is requested. We strongly suggest that for most of urological indications, botulinum toxin should be used by committed interdisciplinary teams of physicians and related health care professionals with appropriate instrumentation to assess the clinical beneficial as well as objective and sub clinical side effects. The long-term effects of chronic treatment with botulinum toxin remain unknown. Prolonged follow-up is necessary in patients on maintenance therapy and an international independent database should be established.

CONCLUSION

Generally new therapies are supposed to be better than the treatment they replace and not to induce any side effects. Studies of an alternative treatment to antimuscarinics for overactive bladder (OAB)

are more likely to cite preliminary studies reporting positive results than equally valid studies, which use the same compounds, with disappointing results. Most of us, generally, have an unwarranted optimism in the efficacy of new therapies and it might represent, or be called, an optimism bias. This mental position, with regard to a state of research in a specific field i.e. overactive bladder therapy, has several serious implications. One is the creation of potentially unrealistic expectations, for both patients and clinicians, of the likely benefits of new treatments such as botulinum toxin. All of us should make emerge a crucial empirical question: what is the prior probability, on average, of a proposed new treatment for OAB or urge urinary incontinence being superior to antimuscarinic agent treatments? The available data seems to suggest that new treatments (vanilloids, nociceptin/orphanin FQ, botulinum toxin) are equally likely to be inferior to standard treatments as they are to be superior. The issue, which remains unsolved, is the fact that new therapies are generally adopted in patients refractory to anticholinergics and this represents a clear selection bias. Furthermore, clinicians need to be aware that optimism is usually both unwarranted and counterproductive when there is uncertainty about the long-term effects of treatments, and of the resulting need to address this uncertainty in clinical trials. On the contrary, in some circumstances it runs the risk of deterring participation in clinical trials designed to reduce genuine and important uncertainties about the effects of treatments, and of discouraging replication of apparently promising early studies. Until these issues are addressed there must remain doubts about whether clinicians involved in trials, which use new drugs, are genuinely observing the outcome and they maintain the ethical requirement of uncertainty.

CONFLICT OF INTEREST

The authors have no conflict of interest. The authors perspective on this topic is a personal one and of necessarily selective bibliography, and cannot do justice to the vast literature about this field.

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