The Future of Erectile Dysfunction Therapy II: Novel Pharmacotherapy and Innovative Technology

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12.1 Introduction

Erectile dysfunction (ED) is defined by the inability to obtain and maintain a penile erection sufficient for satisfactory sexual performance [1]. It is a condition that affects the quality of life of over 150 million men worldwide [2], and in the United States, it is estimated that almost 52 % of men above age 40 experience ED [3]. A major breakthrough in ED treatment occurred in 1998 with the introduction of sildenafil, a selective phosphodiesterase-5 inhibitor (PDE5i) that potentiates the smooth muscle relaxing effects of cyclic guanosine monophosphate (cGMP), allowing for improved erectile response [4]. Since then, PDE5is have been the first line in ED therapy. However, up to 35 % of ED patients may fail to respond to these drugs and move to second- or third-line therapies which have increasing levels of invasiveness [5]; thus, the quest for improved treatments of ED is ongoing [6]. While current treatment modalities have become easier to administer, more scientifically based, and clinically accepted, they still have shortcomings including inconvenience and limited efficacy and spontaneity. Moreover, these therapies do not correct the underlying physiological problem or prevent ED, whereas an ideal therapy would. These shortcomings are well recognized, with many investigators exploring improved methods to meet this objective. Broadly speaking, such directions include novel pharmacotherapy, gene therapies, tissue engineering, and mechanical technologies. Among these directions, some notable progress has been made in the fields of stem cell therapy, gene therapy, internal pudendal artery stenting, vibratory stimulation, growth factors, and low intensity shockwave therapy. These treatment strategies together are advancing the understanding of erection physiology by identifying key molecular targets as well as prime biological constituents. Continued evaluation of these novel therapeutic modalities will bring new options for the man dealing with erectile dysfunction.

12.2 New Treatments for Erectile Dysfunction

12.2.1 Novel Pharmacotherapy

Small molecule and biologically based pharmacotherapy have been the mainstays of erectile dysfunction treatment, from oral medications to intraurethral suppositories and intracavernosal

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(IC) injections. Improved understanding of the mechanisms of erection has identified new targets and avenues for modulating the erectile response. The cell signaling pathways being actively targeted pharmacologically are related to vasodilation (nitric oxide (NO)-cGMP pathways, cAMP pathways) and vasoconstriction (adrenergic pathways, endothelin receptors, angiotensin receptors, and RhoA/Rho kinase).

Given the well-established role of NO in the physiology of erections, there are numerous novel pharmacological therapies targeted at increasing endogenous NO concentrations. A diverse array of strategies is being studied including targeting catalytic enzymes, biochemical cofactors and products, and degradative enzymes. One approach targets the substrate for NO synthases through the administration of L-arginine or inhibiting arginases. Studies in rabbits and diabetic rats provide evidence for improved erectile function and decreased inflammation with administration of L-arginine and analogs [7, 8], as well as studies looking at arginase inhibition [9, 10]. However, it is unclear whether oral administration raises serum levels of L-arginine significantly in humans, although two trials demonstrated some benefit in patients with mild–moderate ED [11, 12]. Another novel strategy targets extracellular signal-related kinase (ERK), whereby inhibition improves cavernosal relaxation in diabetic mice [13]. Of particular interest is the development of guanylate cyclase activators that drive increased cGMP production independent of NO stimulation [14]. In vitro and in vivo studies have demonstrated the benefit of guanylate cyclase activators in various animal models of ED, which increase cGMP production [15, 16]. The pro-erectile effects of these agents are further enhanced with co-administration of PDE5is [17]. These agents are of particular interest in patients who may have impaired endogenous NO release, such as in neurologically impaired patients or those who have undergone prostatectomy. Besides activation of the cGMP pathway, activation of the adenylate cyclase-cAMP pathway has been targeted in the treatment of ED via alprostadil, a cAMP agonist. Adenosine itself is a potent vasodilator and promotes penile erection, although it carries a potential risk for penile fibrosis [18]. As a pharmacotherapy, adenosine is very short-lived and studies looking at intracavernosal injection in men demonstrated increased blood flow but failure to obtain full erections [19].

Strategies targeting vasoconstriction inhibition have made significant progress as well. Recent work has confirmed a major role of the RhoA/Rho-kinase signaling pathway as a dominant regulator of vascular smooth muscle contraction throughout the body as well as in the penis [20]. RhoA/Rho kinase is involved in maintaining the flaccid state through increased noradrenergic tone and has been studied in several animal models [21, 22]. A particular focus of attention for pharmacotherapeutic development is whether the actions of conceivably selective stimulatory or inhibitory binding proteins for this pathway operate in the penis and may be exploited to derive an erectile response specifically and without adverse consequences elsewhere in the body [23]. Several Rho kinase inhibitors improve erectile function in rat models of ED and may do so in the presence of inhibition of nitric oxide synthase (NOS) [24, 25]. Thus, RhoA/Rho kinase represents exciting therapeutic targets in ED. However, findings in animal models have yet to be validated with human trials. Other approaches to suppress vasoconstrictive and anti-erectile mechanisms include α-adrenoreceptor antagonists, endothelin receptor antagonists, and angiotensin receptor antagonists [26]. Several studies demonstrated that selective endothelin receptor A antagonists improve erectile function in animal models of ED [27, 28]. While angiotensin receptors are routinely targeted in the treatment of hypertension with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, there is an increasing body of evidence that purports beneficial effects on erections by improving cavernosal endothelial function [29, 30].

There is great clinical interest in the area of regenerative medicine through the use of growth factors that may offer neuroprotective and vasculoprotective interventions, improving the erectile response that is damaged by neuropathic

disease or injury. An extensive body of work has been accumulated, primarily using experimental rodent models, demonstrating that various neurotrophins and angiogenic factors [i.e., nerve growth factor (NGF), acidic fibroblast growth factor (FIBP), and brain-derived neurotrophic factor (BDNF)] as well as atypical neurotrophic factors such as growth hormone, the morphogenic factor Sonic hedgehog protein (SHH), the cytokine-hormone erythropoietin, vascular endothelial growth factor (VEGF), insulin-like growth factor (IGF-1), and fibroblast growth factor (FGF) play major roles in penile neuronal functions [31–35]. The use of these growth factors is of particular interest in regenerative medicine in scenarios including post-prostatectomy ED. Sonic Hedgehog protein, for instance, promotes cavernous nerve regeneration and improves erectile function after crush injury in animal models and is believed to function in part through the actions of BDNF [36–41]. Angiogenic factors such as VEGF and erythropoietin can promote nerve regeneration, inhibit apoptosis, stimulate cell proliferation, and maintain endothelial function. Local delivery in rabbit and rodent models showed improved recovery of erectile function in castration, diabetes, hyperlipidemia, and peripheral vascular disease models of ED [19]. The idea or restoring or regenerating endogenous mechanisms for erections is certainly an appealing approach; however, human clinical trials have yet to confirm the efficacy of any particular approach.

Overall, novel pharmacotherapy continues to be a fertile ground for future ED treatments with two main approaches underway: pharmacological stimulation/inhibition of pathways involved in the erectile response and regenerative approaches aimed at reversing dysfunction associated with worsening erectile response. RhoA/Rho kinase inhibition is a particularly interesting approach that could be used synergistically with current treatments. However, like other small-molecule therapies, it continues to have the same pharmacokinetic limitations of maintaining adequate blood levels and not treating the underlying disorder. Growth factors offer the promise of reversing the underlying disorder. However, ED tends to be multifactorial and may not be adequately corrected with any one particular approach, and the magnitude of the clinical effect in humans has not been studied. Thus, more work must be done on growth factors to understand their clinical utility and role, be it a limited protective effect when a direct insult is anticipated, such as post-prostatectomy or after radiotherapy, or more widespread use in cases of mild ED.

12.2.2 Mechanical Technologies

12.2.2.1 Internal Pudendal Artery Stenting

Arterial insufficiency is one of the most common etiologies of ED as the penis can be viewed as an extension of the vascular system. Furthermore, ED progression correlates with and often precedes clinical manifestations of vascular diseases, such as coronary artery disease, atherosclerosis, and peripheral vascular disease. However, historical attempts at treating penile arterial insufficiency as a cause of ED through bypass grafts and revascularization procedures were plagued by complications and poor patient selection [26]. Given the lack of clear benefit in ED patients who most commonly suffer from venous leak, as opposed to arterial insufficiency, and the relative high risk of microsurgical vascular reconstructive procedures, the American Urological Association discourages the use of such procedures, except in select situations including otherwise healthy young men with perineal trauma or pelvic fracture [42]. More recently, there have been significant technological advances in the use of interventional procedures to both diagnose and treat stenotic vessels with low risk of complications, such as has been used in coronary artery and peripheral vascular disease. The rationale for the use of stenting in the treatment of ED is that older patients with obstructive atherosclerotic disease who fail to respond to PDE5is may have arterial insufficiency as a significant contributory factor. Furthermore, this subgroup may be identified by angiography in the iliac, internal pudendal, and cavernosal arteries. These stenotic regions are then targeted for dilation and stenting. The Zen

Trial evaluated the use of stents coated with the antiproliferative agent zotarolimus, a derivative of rapamycin (zotarolimus-eluting stent system—Medtronic, Santa Rosa, CA) in patients with internal pudendal artery stenosis [43]. In the trial, 30 patients were treated with drug-eluting stents to the internal pudendal artery after stenosis was identified. All demonstrated significant improvements in peak systolic velocity on duplex studies after the procedure with 14.4 cm/s improvement at 30 days and 22.5 cm/s at 6 months. The primary endpoint was an improvement of ≥4 points on the IIEF-6 ED domain in ≥50 % of subjects, and 59.3 % of patients met this endpoint with no significant complications. Another study looked at balloon dilation of the internal pudendal artery without stenting in a case series of three patients, and patients reported subjective improvement in erectile function [44]. Both studies sought to address the problem of pudendal artery stenosis refractory to PDE5i-mediated smooth muscle relaxation. Another group in Germany sought to treat veno-occlusive dysfunction through selective embolization of veins draining the penis. In a series of 27 patients, the authors reported embolization of the dorsal penile vein with *N*-butyl-2-cyanoacrylate and observed improvements in erectile function in 24 of 27 men with 29.6 % reporting "normal" tumescence and rigidity after the procedure [45].

12.2.2.2 Vibratory Stimulation

While previously mentioned ED therapies focus on potentiating the efferent effects of neural stimulation and downstream vascular responses, vibratory stimulation aims to stimulate afferent nerve pathways, primarily via pudendal-cavernosal reflexes [46]. Vibratory stimulation may provide penile rehabilitative effects that allow for improved erectile responses. Advances in vibratory stimulation led to the introduction and FDA clearance of a handheld vibratory stimulator in 2011. The Viberect (Reflexonic, Chambersburg, PA) provokes penile erections and ejaculation in men through stimulation of the pudendal nerve reflex [46]. Its main role is believed to be through the rehabilitation of nerve tissue through the regular afferent stimulation of nerve fibers. Animal data from male rats and dogs suggests that afferent and efferent pathways via the pudendal nerve branches contribute to the erectogenic response [47, 48]. Preliminary data from clinical trials in spinal cord injury patients [49] as well as non-spinal cord injury patients demonstrate that it is safe and may improve subjective erectile function and urinary incontinence [50], though these studies primarily assessed safety rather than efficacy. Randomized trials and carefully conducted clinical trials are still needed to fully assess the role of vibratory stimulation in the treatment of ED.

12.2.2.3 Shockwave Therapy

Low-intensity extracorporeal shockwave therapy (LI-ESWT) is a novel treatment modality that aims to restore the natural erectile mechanism to allow spontaneous erections. Low-intensity shock wave treatments allow energy transmission through tissue towards a focal point. The basis for this treatment stems from studies done on grafts that demonstrated that sustained treatments of low-intensity ultrasound energy causes microtrauma, which stimulates enhanced angiogenesis and expression of the angiogenic factor VEGF [51]. This in turn results in improved vasculogenic responses to neural stimulation during the erectile response.

Most studies looking at LI-SWT use approximately 300 shocks per treatment point with an energy density of <0.1 mJ/mm^2 at a frequency of 120 per min, though it is not clear if this is the optimal treatment parameters [52]. Wang et al. demonstrated that LI-SWT stimulated angiogenesis-related growth factors including dNOS, VEGF, and endothelial cell proliferation factors and that the resultant neovascularization persisted for greater than 6 months [53]. This was then tested in animal models of erectile dysfunction and indeed showed enhanced VEGF expression with improved intracorporeal pressures with electrical stimulation [51].

In the first study to evaluate the feasibility and safety of LI-ESWT in humans, investigators enrolled men with ED who had a prior positive response to PDE5i therapy. The authors demonstrated safety and a stable improvement in their

IIEF-ED domain scores from 13.5 to 20.9 over the 6-month study period [54]. This same biweekly, 9-week LI-ESWT protocol was used in two additional studies: one evaluating LI-ESWT in severe ED patients who were poor PDE5i responders and a randomized, double-blind sham controlled study looking at efficacy. Both studies demonstrated feasibility and tolerability of the treatment with modest efficacy, at least in the short term [52, 55]. Such a technique is quite promising if the effects are durable. As opposed to existing pharmacotherapy, this approach attempts to counter the underlying causes of ED allowing increased spontaneity and reduced dependence on pharmacotherapy.

12.2.2.4 Mechanical Implants

It is unknown when regenerative ED therapies such as stem cell, gene, and growth factors will be clinically implemented in humans. In addition, there are still limited clinical trial data for low-intensity shockwave therapy and internal pudendal artery stenting. In the meantime, investigators have sought new ways to improve upon existing ED treatments, such as new penile implants and improvements on existing penile implant technology. Penile implants have very high user satisfaction rates and immediately restore the ability to have erections sufficient for intercourse. Researchers are exploring improvements of existing technologies using new materials, improving user experiences through easier pump manipulation, and simplifying the surgery. Other researchers are investigating shape memory materials with properties that offer improved operating characteristics for the patient and the potential of eliminating the pump and reservoir component of the inflatable penile prosthesis [56].

One approach being pursued is the use of nickel–titanium (Ni–Ti) alloys in penile prostheses. These alloys have the desired characteristics of being biocompatible and superelastic and having shape memory properties. By programming the shape memory material to have an expanded cylindrical shape in its activated state, the prosthesis can mimic the erect state of the cavernosal bodies. When deactivated, the material becomes more flexible and mimics the flaccid state. The process of activation can be through direct heat, external magnetic induction using a handheld device, or a small electrical current. In one study, the Ni–Ti alloy was directly compared to existing prosthetic devices and was found to have similar and sometimes superior mechanical properties to existing penile prosthetic devices [57]. Furthermore, since the transition changes occur with realignment at the molecular level, no hydraulic mechanism is necessary, eliminating the pump and reservoir and allowing a profile similar to current malleable devices, but with the operating characteristics of inflatable prostheses.

Mechanical technologies are quite variable in their approach to the treatment of ED. Some are rehabilitative, as in the case of shock wave therapy and vibratory stimulation, while others address the vasculogenic response or offer significant improvements over existing mechanical treatments. The main advantages of the rehabilitative approaches are that they allow spontaneity, have a low risk profile, and may avoid the use of medications. The disadvantages are the need for repeated treatment sessions using specialized equipment, and the durability of the effect and the need for re-treatment are unknown. Internal pudendal artery stenting targets a subset of ED patients that have internal pudendal artery stenosis as well as ED. The advantages are that it allows a one-time treatment to improve erections and may work with other therapeutic options. The disadvantages are that it may only work for a limited subset of ED patients and the duration of the effect is not known. Despite these limitations, mechanical approaches offer a significant alternative to biochemically based approaches that may be used in combination therapies.

12.3 Conclusions

Significant progress has been made in our understanding of the complex physiology of erections, which has allowed more scientifically based treatments to emerge. Though novel pharmacotherapies are being actively pursued, alternative approaches that aim to improve blood flow, regenerate tissue, and restore cell populations provide exciting therapeutic options for the future.

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Commentary: The Future of Erectile Dysfunction Therapy II—Novel Pharmacotherapy and Innovative Technology

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Men with erectile dysfunction (ED) commonly visit their physician first when seeking treatment and are often prescribed medical first-line therapy for their ED. However, these therapies are incompletely effective, and there is a growing understanding that ED, even when organic in origin, has a psychosocial component. This psychosocial contribution is often overlooked or not known by treating physicians. As a result, treatment escalation in most men with ED often remains focused on medical, and finally surgical, therapies, at which point psychotherapy is moot. It is imperative that clinicians understand that ED has psychological ramifications and do not lose sight of the positive effects of incorporating psychotherapy into the treatment of these men. Such a combined therapeutic approach may improve the response to both medical and psychotherapies and decrease the need or dosage of medical therapies.

While Burnett and Kovac focus on the future of ED therapy from a medical perspective in their chapters, a truly comprehensive understanding of the future of ED therapy incorporates an understanding of psychotherapeutic approaches as well. As such, the following commentary highlights psychosocial cultural factors and corresponding mental health approaches to ED that, when applied in combination or in lieu of medical therapies, will optimize ED therapy. A combined, collaborative approach to ED therapy, irrespective of the medical therapy, truly represents the future of ED therapy.

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Commentary

Brian V. Le and Arthur L. Burnett's chapter provides an excellent overview of future opportunities for erectile dysfunction (ED) treatment from a biological point of view with its emphasis on the probable emergence of novel pharmacotherapies, growth factor and stem cell therapies, and mechanical technologies. Le and Burnett also touch on the potential for some of those therapies to be combined with both each other and existing medical treatments to enhance efficacy beyond what is currently available today. However, an appreciation for the additional improvements that a psychosocial-behavioral and cultural (PSBC) paradigm would provide has eluded mention in their chapter and others in this text. Such an integration is not only key to optimizing efficacy; it can also improve treatment safety as drug dosage can be reduced with the inclusion of non-pharmaceutical factors that enhance response to ED treatment. The benefits and rationale for using an integrated treatment approach were partially elucidated in chapter one and have been described extensively elsewhere [1, 2]. An integrated approach can be easily understood using a number of dual control paradigms. However, the Sexual Tipping Point (STP®) model is especially useful when it comes to illustrating integration of future medical modalities within a biopsychosocial-behavioral and cultural model (see Fig. 1.2, 1.3, 1.4). In short, the STP® model provides a conceptual framework for an optimized, integrated treatment approach for every novel future therapy summarized by Le and Burnett.

All cases of ED can be considered of "mixed" etiology, with contributions from both organic and PSBC components [3, 4]. Sachs suggests that there are "neural, neurochemical, and endocrine mechanisms whose participation in erectile function depends on the behavioral context in which erection occurs" [5]. Thus, optimal therapy for ED, and for any sexual dysfunction for that matter, should be approached with an understanding that both the physical and mental aspects of the sexual dysfunction are essential contributors to the pathology and that addressing both facets of the condition will offer the most significant improvements [6]. To provide an example using existing treatments, discontinuation rates of phosphodiesterase 5 inhibitor (PDE5i) therapies in men with ED approach 50 % [7], but 18 % of men who discontinue PDE5is have psychological factors that can readily be addressed using combination therapy [8–12]. Other psychosocial factors, including a couple's dynamics, a man's approach to sex with his partner, and the couple's expectations of the effects of the medical intervention in their love life, are often less obvious to the physician, but are nevertheless essential in restoring full sexual function and are often not considered [13]. By extrapolating from studies of men undergoing psychotherapy where erectile function improvements were observed in the absence of medication [14, 15], as well as examining response rates of ED to placebo in randomized clinical trials (RCTs), it is reasonable to predict that all of the novel treatments Le and Burnett describe could be "dose" titrated down to improve safety profiles when attention to PSBC variables is integrated into the treatment approach. Support for such integration may be found by examining early reports of adjunctive sex therapy for men suffering from organic ED who underwent penile prosthesis placement. Counseling helped set expectations and facilitated the integration of the prosthesis into the sex life of the couple and often resulted in increased patient and partner satisfaction [16–21]. Much recent work argues for an integrative treatment approach in men with ED, and steady progress towards this goal is being made [9, 11, 22–25].

A transdisciplinary approach, whether offered by a solo practitioner or a multidisciplinary team, should always be considered, even as other improvements in systems medicine stand to revolutionize treatment of ED and other sexual dysfunctions [2]. A primary care practitioner (PCP) or urologist may integrate sex counseling with the use of pharmacotherapy in their treatment of ED within the limits of their skill set and available time. The most important PSBC factors can frequently be identified during the course of a proper diagnostic interview using standard techniques for obtaining a focused sexual history and

current sex status [26]. However, a collaborative approach, whether using a virtual or in-house team involving sex therapists and the patient's medical care team, will further facilitate and improve care of these patients, particularly in cases with moderate or severe psychosocial complexity where the principle etiologic factors of the patient's ED lie outside the primary provider's expertise [18, 27]. There is even evidence, which only future research will confirm, that such behavioral and cognitive interventions change brain chemistry and neuropathways in a manner that makes success more continuous and minimizes risk of relapse.

Like all medical interventions, future therapy for ED must consider and should rely on a patient-centered approach, guiding treatment based on a patient's goals [12, 18, 28]. Involvement of the patient's partner in the assessment and treatment process is almost always preferable [29]. Yet, urologists who frequently see the man for treatment alone may find it comforting that sex therapy research supports partner cooperation, rather than attendance at each office visit, as the key to treatment success [21]. Nonetheless, regardless of the development and deployment of novel effective and safe approaches to ED, all clinicians are well reminded to emphasize patient and partner pleasure and satisfaction over objective performance, as exemplified by the "Good Enough Sex" model by Metz and McCarthy [30]. Again, the use of a "sex status" examination, which focuses on identifying all the key factors relating to the patient's ED, is critical in comprehensively understanding the landscape of the patient's problem and can help to identify appropriate medical and psychosocial interventions, highlighting the utility of an integrative approach [24]. Of course, the need for patient education and regular follow-up cannot be emphasized enough regardless of treatment novelty, as these facilitate adherence to treatment [11, 31, 32].

In much the same way that Le and Burnett describe exciting targets for both selective inhibition and stimulation of binding proteins that would facilitate erectile activity without adverse consequences elsewhere in the body, psychosocial-behavioral interventions derived from traditional sex therapy, cognitive behavior therapy, and systems approaches all help optimize the efficacy of these future pharmaceutical interventions [1]. Several key signaling pathways and molecules, including nitric oxide (NO) synthases and endogenous NO levels, the angiotensin receptor, extracellular signal-related kinase (ERK), guanylate cyclase modulators, and Rho/RhoA kinase, are highlighted by Le and Burnett as novel pharmacotherapeutic targets. While these pathways and molecules are critically important in the physiologic ability to initiate and maintain an erectile response via positive and negative influences on their respective pathways, and thus the STP®, one must also consider the psychological processes acting through a cascade of central effects, which further influence the STP®. Like PDE5is, sexual stimulation (both mental and physical) will likely potentiate the action of pharmacotherapies targeting the above pathways [15], further highlighting the mind-body connection in sex.

As one contemplates an integrative model, enhancement of arousing factors and minimizing of inhibiting factors must be considered. When discussing growth factors, Le and Burnett focus on neurotrophic and angiogenic factors that are now known to play major roles in penile function and may be of particular interest in situations where damage to the cavernosal nerves occurs, such as post-prostatectomy. Similar to the considerations with pharmacotherapies, each growth factor functions by stimulating a specific physiologic pathway, resulting in improved penile function and exerting a positive influence, tipping the STP® balance scale towards greater sexual responsiveness. While penile physiology may improve using medical treatment, the psychological grief and adjustment that is often an integral part of post-prostatectomy ED [33] is clearly an inhibitor, which is often best addressed using counseling alone or in combination with pharmacotherapy [34].

Although stem cell therapies are oriented towards replacing nonfunctional tissue to restore the natural processes that facilitate erection rather than modulating existing pathways, their impact

on physiology likewise integrates excitatory and inhibitory functions and fits into the STP® model, much like the effects of the other medical therapies described by Le and Burnett. Similarly, pudendal artery stenting, low-intensity extracorporeal shock wave therapy (LI-ESWT), and penile vibratory stimulation also improve penile physiology and help to maximize physical potential, but in the absence of optimized psychosocial-behavioral and cultural factors, the patient's STP® may remain closer to "Not" than "Hot," and his true potential remains unmet.

Finally, experimental design is an additional relevant factor that should be considered when evaluating all the exciting potential new treatments for ED described by Le and Burnett. Specifically, advances in understanding the placebo effect and its application to sexual disorders are important considerations [35, 36]. One of the most important elements that psychology brings to medical and pharmaceutical evaluation is the notion of placebo, placebo response, and placebo effect. We should remain mindful that these variables impact our studies and that careful scientific evaluation requires an understanding of these concepts. It is well known that responses to placebo often well exceed 20 % in RCTs evaluating ED treatments. Evidence has also surfaced in some psychiatric drug trials that the therapeutic setting and frequency of visits can account for over 50 % of observed positive responses. To what extent is this true for clinical trials in sexual medicine? It makes intuitive sense that more frequent contact and follow-up with patients may contribute to better responses, and this is supported by the relapse prevention literature [37]. In fact, this effect is even more pronounced in older adults, the very demographic more likely to be suffering from ED [36]. It would be extraordinary if we could better understand how to minimize the placebo effect, particularly in clinical trials, and maximize it during treatment! That indeed would be the type of elegant advance resulting from integration of knowledge from two seemingly disparate areas of science. Yet the benefit to researchers, clinicians, and patients alike would be both remarkable and profound.

In conclusion, it is our belief that almost every sexual experience, whether or not facilitated by a pharmaceutical (or alternative technology), could be enhanced by an increase in erotic thought, a reduction in distracting negative intrusive cognitions, and better quality and pleasing "friction." Improving these elements or more simply put increasing "friction and fantasy" has been advocated by sex therapists for decades [11]. Reciprocally, identifying and successfully targeting key signaling pathways and molecules in the manner outlined by Le and Burnett will improve the erectile capacity of men well beyond the early successes of the last 20 years. The STP® model provides a framework for understanding the subtleties of the combined and variable effects of physiology and psychobiology in sexual function. Such an understanding that addresses all factors involved in the dysfunction will truly optimize, and in the future revolutionize, treatment of ED and other sexual dysfunctions. Integrating medical therapy and counseling potentiates the individual approaches, and the sum of the parts is significantly greater than each part alone (see Fig. 1.4).

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