

Review Article

Evidence Synthesis from Cochrane Reviews and Non-Cochrane Reviews and International Guidelines about the Effectiveness of Psychosocial Interventions for the Treatment of Erectile Dysfunction (ED) Compared to Oral Drugs, Local Injection, Vacuum Devices and Interurethral Alprostadil

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Abstract

There is high-quality evidence that have shown the negative psychosocial impact of erectile dysfunction (ED) in quality of life, affective and marital relationship. However, whether to indicate psychosocial interventions are still matters of controversy. This study aimed to compile evidence systematically from Cochrane reviews and non-Cochrane reviews and International Guidelines of effectiveness of psychosocial interventions for the treatment of ED compared to oral drugs, local injection, vacuum devices and interurethral alprostadil. We have summarized the published evidence of: two Systematic reviews (SR), one Cochrane SR and four International Guidelines. We assessed the methodological quality of the three included SRs using AMSTAR. Association of PDE-5 and psychotherapy was more efficacious for ED symptoms than PDE5-I treatment alone according two metanalysis, in Cochrane SR the effect size was (RR 0.46, 95% CI 0.24 to 0.88; NNT 3.57, 95% CI 2 to 16.7, N = 71), and were less likely than those receiving only PDE5-I to drop out (RR 0.29, 95% CI 0.09 to 0.93). Group psychotherapy was more likely than waiting list to reduce the ED at post-treatment (RR 0.40, 95% CI 0.17 to 0.98, N = 100; NNT 1.61, 95% CI 0.97 to 4.76). No differences in effectiveness were found between psychosocial interventions versus local injection, interurethral alprostadil and vacuum devices. According EUA Guideline psychosocial interventions are one the few curative treatments for psychogenic ED and can save patients of long standing and expensive therapies. However, these findings require confirmatory large and well design clinical trials to ensure efficacy at long term follow-up and in subgroups of patients with ED.

INTRODUCTION

Erectile dysfunction (ED) has been one of most prevalent sexual dysfunction in the last decades [1,2]. Epidemiological data have shown a high prevalence and incidence of ED worldwide [1,3]. Aytaç et al. 2011 [2], considered the United Nations projected male population distributions by quinquennial age groups for 2025, and the prevalence rates for ED were applied

from the Massachusetts Male Aging Study (MMAS) to calculate the likely incidence of ED. The projections for 2025 show a prevalence of \approx 322 million with ED, an increase of nearly 170 million men. The largest projected increases were in the developing world, i.e. Africa, Asia and South America.

According to a systematic review of population based studies, the prevalence of erectile dysfunction (ED) ranges from 2% in

men younger than 40 years to 86% in men 80 years and older [3]. In the US, the mean overall prevalence of ED in men over 19 years of age is 18.4% (95% CI 16.2 to 20.7), which means that ED affects 18 million men (95% CI 16 to 20) in that country alone ⁴.

Recent data show that psychological aspects are involved in a substantial number of cases of ED alone or in combination with organic causes [5-7]. There is reliable, high-quality evidence that have consistently shown the negative psychosocial impact of ED in affective and marital relationship promoting feeling of guilt and denial, depression, anxiety, decrease in self-confidence and self-esteem [7-9]. Results from epidemiological studies have convincingly demonstrated that ED linked to negative impact in professional activities, social interactions and quality of life [5]. Psychotherapy looks at two primary areas to assess ED and intervene therapeutically. Individual issues may include performance anxiety, depression, lack of sexual knowledge, sexual fears and inhibitions, shame, guilt, and intimacy issues. Issues within a relationship which may lead to erectile dysfunction include unresolved conflicts, communication difficulties, lack of knowledge, and unwillingness to experiment with new behavior [7]. Once the individual or relationship issues which are causing or contributing to ED are identified, psychosocial interventions can provide mechanisms to manage or solve these issues to restore erectile function [6].

However, whether to indicate psychosocial interventions for ED are still matters of controversy, because in contrast to the many publications on pharmacological agents, the number of studies on psychotherapy for the treatment of ED is relatively small [4,5,7-9].

Besides that, with a growing population of men who are initially refractory or become refractory to PDE-5 inhibitors the indication of PDE-5 as first line treatment for ED results showed that one in three men discontinue treatment with a PDE5 in some cases after the first prescription [10-13]. In one study, 54 (35%) of 156 patients with remission of ED using sildenafil discontinued treatment after 6 months. Reasons included patients and/or partners not being emotionally ready to resume sexuality after a long abstinence (37%); concerns about adverse effects (18%); return of spontaneous erections (15%); unwillingness to accept a 'drug-dependent erection' (7%) and either the unacceptability of planned sexual activity or lack of sexual interest (4% each) [12].

Why it is important to do this evidence based synthesis

Considering this scenario, the importance and main purpose in this brief communication is to compile evidence systematically from Cochrane reviews and non-Cochrane reviews and international Guidelines of effectiveness of psychosocial interventions for the treatment of ED compared to oral drugs, local injection, and vacuum devices and interurethral alprostadil into a single comprehensive and user-friendly document for clinician and researchers. We also summarized gaps in the evidence base that will inform recommendations for new research and reviews.

METHODS

We included Cochrane reviews, non-Cochrane reviews and recent Guidelines. We searched the Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effect,

PROSPERO International prospective register of systematic reviews and PubMed. The search is current November 2016 (covering from 1980 to November 2016).

The main reasons for exclusion were ineligible study design (non-systematic reviews, guidelines and randomized controlled trials) and ineligible interventions such as for example phytotherapy.

We also identified trials that were potentially eligible for, but not currently included in, published reviews to make recommendations for new systematic reviews and these trials were described in implications for future research.

Selection of reviews

Two review authors (TM and SG) independently assessed systematic reviews and guidelines for inclusion. There was no disagreement, so discussion with a third person was not needed (KPS).

Data extraction and management

We extracted data from studies included in the existing Cochrane reviews and non- Cochrane Reviews in relation to the characteristics and data for the outcomes.

Assessment of methodological quality of included reviews

Quality of included reviews: We assessed the methodological quality of included reviews using the following criteria adapted from AMSTAR (Assessing the Methodological Quality of Systematic Reviews) [14].

- Was an a priori design provided?
- Was there duplicate study selection and data extraction?
- Was a comprehensive literature search performed?
- Were published and unpublished studies included irrespective of language of publication?
- Was a list of studies (included and excluded) provided?
- Were the characteristics of the included studies provided?
- Was the scientific quality of the included studies assessed and documented?
- Was the scientific quality of the included studies used appropriately in formulating conclusions?
- Were the methods used to combine the findings of studies appropriate?
- Was a conflict of interest stated?

AMSTAR was rated: more than 8 points (high quality), 4 to 7 (moderate quality), 3 or lower (low quality). A review that adequately met all of the 11 criteria was considered to be a review of the highest quality [14].

RESULTS

The broad literature searches in all relevant databases for systematic reviews: Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effect, and PROSPERO

International prospective register of systematic reviews and PubMed were used in this overview has captured all the published systematic reviews and guidelines. The search strategy (psychotherapy or psychosocial and erectile dysfunction) identified 127 records and four guidelines; after removal of duplicate references there was a total of 11 records considered for this evidence synthesis. Figure (1) details the screening process.

We have summarized the published evidence as outlined of two Systematic reviews [15,16] and one Cochrane review [7]. Four recent guidelines are also included: European Association of Urology [17]; Canadian Urological Guidelines Committee: Erectile dysfunction Practice Guidelines [18]; American Urological Association ED guideline [19] and the Guideline on Erectile Dysfunction of the Brazilian Medical Association [20].

Cochrane Reviews and others systematic reviews

Melnik et al. [7], in a Cochrane review and meta-analysis to assess the effects of psychosocial interventions for men with ED compared to oral drugs, local injection, vacuum devices, interurethral alprostadil and other types psychosocial interventions reported that there was evidence that group psychotherapy may improve erectile function compared to waiting list (no-treatment).

This Cochrane Review included nine randomized controlled trial (RCTs) and two quasi-randomized trials involving 398 men with ED (141 in psychotherapy group, 109 received medication, 68 psychotherapy plus medication, 20 vacuum devices and 59 control group) met the inclusion criteria. In data pooled from five randomized trials group psychotherapy was more likely than the control group (waiting list - a group of participants who did not receive any active intervention) to reduce the number of men with "persistence of erectile dysfunction" at post-treatment (RR 0.40, 95% CI 0.17 to 0.98, N = 100; NNT 1.61, 95% CI 0.97 to 4.76) [6].

At six months follow up there was continued maintenance of reduction of men with "persistence of ED" in favor of group psychotherapy (RR 0.43, 95% CI 0.26 to 0.72, N = 37; NNT 1.58, 95% CI 1.17 to 2.43). In pair-wise meta-analysis that included two RCTs that compared group therapy plus sildenafil citrate versus sildenafil, men randomized to receive group therapy plus sildenafil showed significant reduction of "persistence of ED" (RR 0.46, 95% CI 0.24 to 0.88; NNT 3.57, 95% CI 2 to 16.7, N = 71), and were less likely than those receiving only sildenafil to drop out (RR 0.29, 95% CI 0.09 to 0.93). However, these findings require confirmatory large and well design clinical trials to ensure efficacy at long term follow-up and in subgroups of patients with ED. No differences in effectiveness were found between psychosocial interventions versus local injection, interurethral alprostadil and vacuum devices [7].

Hernando-Berríos [15] performed a SR that included men with ED who had received non-pharmacological and non-surgical intervention for ED. The authors included free-access, complete texts with an available summary published between 2000 and 2006. Studies not published in English were excluded, this can limit the confidence in the results of this SR due a publication bias. Similarly, to Cochrane review findings the authors

found the non-pharmacological and non-surgical intervention may help to improve or reverse ED and guarantee satisfactory and lasting results. This review also concluded that more well design RCTs are need to confirm these findings.

Schmidt and colleagues [16] conducted SR and included RCTs and controlled trials comparing psychosocial interventions with PDE5-I treatment or one of them against a combination of both. The period of the searches considered studies published between 1998 and 2012. Eight studies with a total number of 562 patients were included in the meta-analysis. The meta-analysis found that, overall, combined treatment was more efficacious for ED symptoms than PDE5-I treatment or psychosocial interventions alone. Combined treatment was more efficacious than PDE5-I use alone on sexual satisfaction. No differences were found between PDE5-Is and PI as stand-alone treatments. None of the moderators (treatment duration, methodological quality, or researcher allegiance) altered the effects. The authors concluded that the combination of psychosocial interventions and PDE5-Is is a promising strategy for a favorable outcome in ED and can be considered as a first-choice option for ED (Table 1).

Guidelines

The European Association of Urology Guideline [17] on Male Sexual Dysfunctions stated can be treated successfully with current treatment options, but it cannot be cured. The only exceptions are psychogenic ED which potentially can be cured with the patient receive psychotherapy. Also EAU Guideline stated that men with psychogenic ED should receive psychotherapy alone or with another therapeutic approach. Finally, EUA Guideline considered that psychosexual therapy requires "ongoing follow-up and has had variable results" [17].

The American Urological Association Guideline on the Management of Erectile Dysfunction did not review the literature on psychogenic ED, however it stated that combined approach that's include psychosexual in combination with pharmacological and surgical intervention may benefit men with ED. The AUA Guideline also mentioned that for some subgroups of men brief education, support, and reassurance may be enough for ED remission and for others, referral for "more specialized and intensive counseling may be necessary" [19].

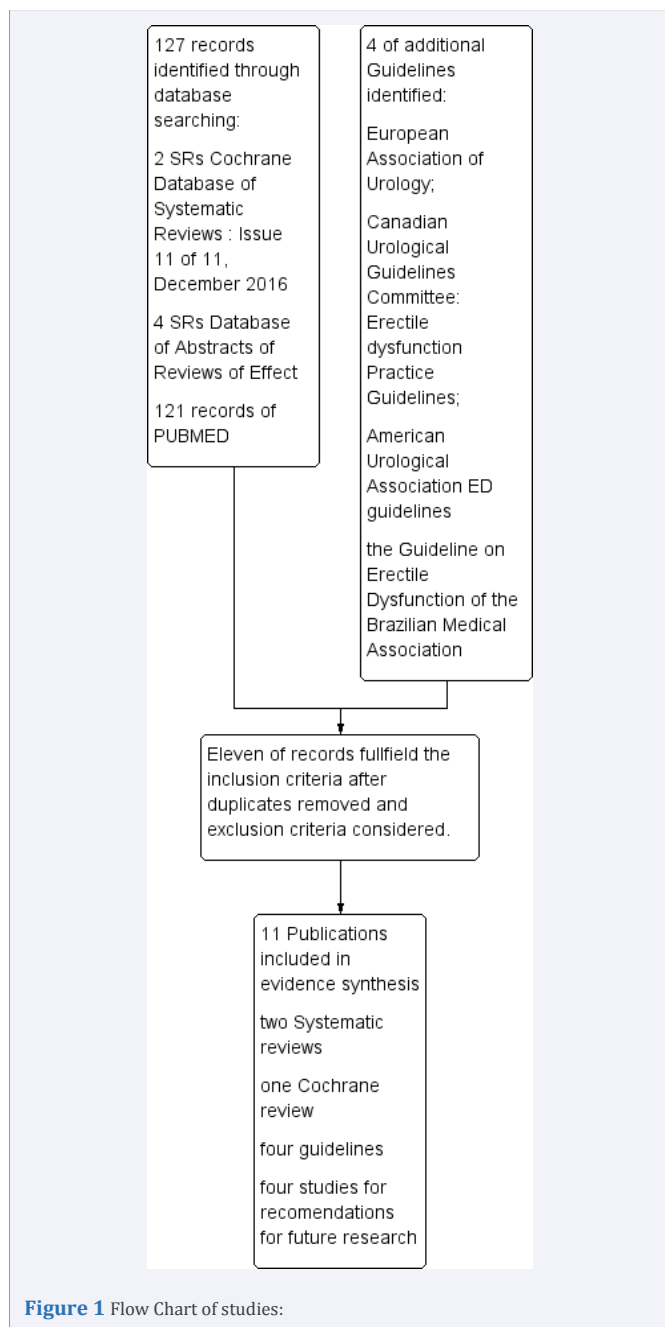
The 2015 Canadian Urological Association Practice guidelines for erectile dysfunction stated that psychological or psychiatric evaluation are very important in management of ED and provide important information into relationships and situational causes to ED. The lack of widespread availability and cost limit their use in most cases of ED treatment. The primary goals of psychotherapy are reduce: performance anxiety, lack of sexual knowledge, sexual fears and inhibitions, shame, guilt, and intimacy issues. . Psycho-education is also important to modify sexual scripts, and to reduce premature drop-out of medications. This guideline defines sexual counseling as a spectrum of approaches from a simple open discussion with the primary care physician to psychologist, sexual therapists and/or psychiatrists [17].

The Guideline on Erectile Dysfunction of the Brazilian Medical Association stated that the benefits of the exclusive psychotherapy or psychotherapy associated to PDE-5 inhibitors are similar and both should be considered on the treatment of psychogenic ED [20].

Table 1: Descriptions of the included Reviews.

Reference	Studies included	Aim	Comparisons	Effect Size	Conclusions	Quality of SR (AMSTAR)
Melnik and colleagues (2007)	11 (9 RCTS and 2 quasi-RCTS involving 398 men with ED)	Assess the effects of psychosocial interventions for men with ED compared to oral drugs, local injection, vacuum devices, interurethral prostadil.	This SR compared different techniques of psychosocial interventions (Rational emotive therapy, psychoeducation, group psychotherapy, cognitive-behavioral sex therapy, behavior therapy group, systematic desensitization, sexological counseling, Relationship therapy and Masters sex therapy) to oral drugs, local injection, vacuum devices, interurethral prostadil.	<ul style="list-style-type: none"> Group psychotherapy was more likely than the control group to reduce the number of men with ED at post-treatment (0.40; 95% CI; 0.17 to 0.98). Association of PDE-5 and psychotherapy was more efficacious for ED symptoms than PDE5-I treatment alone (RR 0.46, 95% CI 0.24 to 0.88; NNT 3.57, 95% CI 2 to 16.7, N = 71) The follow up showed a continued maintenance of reduction of men with ED in favor of group psychotherapy (RR 0.43; 95% CI; 0.26 to 0.72) 	Group psychotherapy was more efficacious than no-treatment (waiting list); Group therapy plus sildenafil showed significant improvement in successful intercourse than those receiving only sildenafil; No differences in effectiveness were found between psychosocial intervention versus local injection and vacuum devices.	High Quality attend all the AMSTAR criteria's
Hernando-Berríos and colleagues (2008)	8 (5 quasi-RCTS, 1 RCTS, 1 correlational study and 1 descriptive study)	Review current evidence about the Non-pharmacological and non-surgical intervention for ED.	This SR compared interventions Non-pharmacological and non-surgical intervention (change in lifestyle, psychotherapy, psychoeducation, multimedia methods and pelvic muscle exercises) excluding studies that included individuals with organic ED undergoing medical or surgical intervention.	Not performed a quantitative analysis	Alternative therapies are available for men with ED; Low quality of studies about non-pharmacological therapies. The Non-pharmacological interventions (change in lifestyle, psychotherapy, psychoeducation, multimedia methods and pelvic muscle exercises) help to improve or reverse ED and ensure satisfactory and long-term results when compared with invasive treatments (oral drugs, local injection, vacuum devices).	Low Quality - Limit literature search and language of publication, included observational studies, no assessment of publication bias, not used appropriate methods to combine findings of studies
Schmidt and colleagues (2014)	8 (6 RCTS and 2 controlled trials involving 562 men with ED)	The aim was to compare the Psychological Intervention with phosphodiesterase-5 inhibitors (PDE5-I) treatment or one of them against a combination of both.	This SR compare Psychological Intervention (psychological intervention, counseling, group psychotherapy, sex therapy, couple therapy, cognitive-behavioral sex therapy, (Internet - based cognitive-behavioral therapy), psychoeducation and sex education) with PDE5-I alone or combine with psychotherapy.	<ul style="list-style-type: none"> Effects on ED Symptoms: the combined treatment yielded a significant additional effect on ED symptoms compared with PDE5-I use alone (0.45; 95% CI; 0.02 to 0.89) Effects on Sexual Satisfaction: The combined treatment yielded a significant additional effect compared with PDE5-I use alone (0.31; 95% CI; 0.00 to 0.61). The overall findings of this meta-analysis suggest that the shortest PI combined with PDE5-I treatment was superior to PDE5-I use alone (0.64; 95% CI; 0.10 to 1.18). 	The findings suggest that the combined treatment was more efficacious when compared with PDE5-Is or PI alone, on ED symptoms and sexual satisfaction in men with ED.	Moderate quality - limit inclusion of published and any unpublished studies included irrespective of language, not used the scientific quality of the included studies appropriately in formulating conclusions.

Abbreviations: RCTs: Randomized Controlled Trials; SR: Systematic Review; CI: Confidence Interval; RR: Relative Risk; OR: Odd Ratio; NNT: Number Necessary to Treat



Implications for clinicians and researchers

Where do clinicians go from here? The challenge and the opportunity are to reconcile population and individual evidence based treatment approaches through the tools of evidence based medicine.

Some steps are important in ED treatments: a) Sexual affective anamnesis b) evidence based standardized scales preferentially perform by multidisciplinary team c) psycho education of the patients and partners to ensure realistic expectations of sexual performance and the treatment; d) prescribing an evidence based treatment considering the etiology, the characteristics of the men and his partner and preferences; e) optimizing treatment by scheduling follow-up visits f) treating comorbidities via lifestyle

counseling, psycho education medications and/or referrals and g) helping men and their partners to address their health and psychosocial issues [13].

To improve adherence to the therapies that work in ED, one approach is psycho education that might help to resolve psychological problems encountered by ED patients. Recent Guideline of European Association of Urology [17] recommended the combination of psycho education and ED therapy for men with ED. Advances in health technology can help in improving adherence, text messaging reminders and virtual health coaching are just a few ways in which men with ED can be engaged in shared decision making. In a digital platform, men with ED can query the concepts of social networking with peers may also be valuable in understanding and promoting psycho education, drug and lifestyle adherence [21-23]. Internet delivery treatments can be a potential relief to the large proportion of men who would like treatment for ED, but who are afraid or embarrassed to look for a specialized help.

McCabe and Althof [6] and Melnik et al. [7,9,10,24], pointed that ED treatment is associated with substantially broader aspects of a man's life than just erectile functioning. McCabe and Althof 2014 conducted a review and demonstrated the importance of evaluating the psychosocial factors associated with ED and its treatment, and the importance of using standardized scales to conduct this evaluation.

This evidence synthesis clearly points to significant opportunities for further research. The role of discovery science in developing more effective treatment cannot stop.

Where do researchers go from here?

First of all is important to mention that that non-statistically significant does not mean that there is no effect of an intervention. Large randomized trials with longer follow ups are necessary to examine whether psychosocial interventions alone can help patients with ED. Considering the quality and amount of evidence for the other comparisons assessed, future research also need to compare psychosocial interventions to oral drugs, local injection, vacuum devices, interurethral alprostadil and penile prosthesis. These studies would need to take into account the study setting, as this may have a confounding effect on the results. A question that needs to be answered is whether a specific type of psychosocial intervention is more effective than others [7].

Internet delivery psychotherapy is as promising treatment modality and large and well design randomized controlled trials are needed. Additionally, future studies need to assess whether effectiveness of the treatment is influenced by personality factors, psychiatric comorbid conditions, duration of therapy, severity of ED and patient's preferences outcomes.

CONCLUSIONS

There is a consensus about the benefits of multidisciplinary approach of ED. According International guideline it is worthwhile to remind that psychosocial interventions are one the few curative treatments for psychogenic erectile dysfunction and when well used can save patients of long standing and expensive therapies [17].

Evidence from two meta-analysis suggested that combination of psychosocial interventions and PDE5-Is is a promising strategy for a favorable outcome in ED. One meta-analysis concluded that group psychotherapy was more likely than waiting list to reduce the ED at post-treatment. However, these findings require confirmatory large and well design randomized controlled trials to ensure efficacy at long term follow-up and in subgroups of patients with ED. No differences in effectiveness were found between psychosocial interventions versus local injection, interurethral alprostadil and vacuum devices.

CONTRIBUTIONS OF AUTHORS

TM- conceived the manuscript, carried out searches, selected reviews for inclusion, assessed methodological quality, extracted data and wrote the final version.

KPS-extracted data and prepared the tables.

SG- extracted data, assessed methodological quality, and acted as arbitrator if necessary and wrote the final version.

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