Evidence Review for Surrey Prescribing Clinical Network

Treatment: Oral and non-oral combination therapy for erectile dysfunction

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1. Purpose of the Review

In March 2012 the prescribing clinical network considered a number of papers relating to treatments for erectile dysfunction:


APPENDIX H APC 08-2012 PDE5 ED.doc


APPENDIX I Intracavernosal inj


APPENDIX J inMOBBB_Policy_47_Er

The following policy statement was issued:


PCN 08-2012 ED.pdf

It was noted that the above papers did not consider combination therapy: an oral phosphodiesterase type-5 inhibitor (PDE5 inhibitor) with a prostaglandin E1 intracavernosal injection / intraurethral instillations.

This paper considers the use of oral PDE5 inhibitor in combination with a prostaglandin E1 intracavernosal injection / intraurethral instillations.

2. Appropriateness

Combination therapy could be considered in a patient with erectile dysfunction who did not respond / had sup-optimal response to monotherapy with an oral PDE5 inhibitor or a prostaglandin E1 intracavernosal injection / intraurethral instillations.

As in other areas of medicine where multiple drugs with different mechanisms of action are combined to more effectively treat a condition this approach has been considered for erectile dysfunction.

3. Effectiveness

Combination of PDE-5 Inhibitor and Intraurethral Prostaglandin

Intraurethral alprostadil and PDE-5 inhibitors may be combined to treat oral monotherapy failures / intraurethral monotherapy failures. This combination maintains the minimally invasive nature of therapy because the prostaglandin does not need to be injected.
In a retrospective study of 63 patients, Mydlo and colleagues[1] reported on the efficacy of combination therapy in men who had failed monotherapy of both sildenafil and intraurethral alprostadil with 18 months of follow-up. Combination therapy where

50% of patients were post prostatectomy consisted of 100 mg of sildenafil 1 hour before intercourse followed by 1000 µg of intraurethral alprostadil 10–15 minutes before intercourse. IIEF scores improved 114% over baseline (10.8) with combination therapy versus 41% and 77% improvements on intraurethral alprostadil and sildenafil monotherapy, respectively. Intercourse satisfaction and overall satisfaction scores on the IIEF domains showed comparable improvements of 125% and 128% over baseline. No serious adverse events were reported. The most common adverse events in decreasing order were urethral burning (30%), throbbing (20%), headache (17%), nausea (12%), increased glans sensation (14%), dizziness (9%), dyspepsia (11%), and blue vision (6%). All symptoms were described as mild, and no patient discontinued treatment due to adverse events, with no priapism reported. Socioeconomic status, education, and cost were theorized as factors impacting long-term results.

Raina and associates[2] evaluated the sildenafil-intraurethral alprostadil combination in 23 men at least 6 months post radical prostatectomy who were unsatisfied with sildenafil monotherapy of 100 mg. One hour after 100 mg of sildenafil, the men were instructed to insert 500 µg of intraurethral alprostadil. If no response was obtained, the dose was increased to 1000 µg. Nineteen of these 23 men (83%) reported improvement in rigidity and sexual satisfaction. The rate of rigidity score and successful vaginal penetration increased from 38% and 50% to 75% and 70%, respectively. Spousal satisfaction improved from 52% to 69%. Urethral burning was the most common side effect and was transient. No serious side effects occurred, and none of the men discontinued treatment due to side effects.

Nehra and colleagues[3] evaluated 28 patients, 17 post radical prostatectomy (less than 5 months from surgery) and 11 with organic erectile dysfunction, who had failed either sildenafil or intraurethral alprostadil 1000 µg monotherapy. All patients reported an improvement in their erections and were able to perform vaginal penetration with a mean of 3.6 intercourse episodes per month. All were continuing combination therapy at 30 months, with some able to reduce their dose of sildenafil from 100 to 50 mg. None had crossed over to injection therapy or penile prosthesis. No patients experienced postural hypotension, priapism, abnormal electrocardiograms, angina, or peripheral vascular complications.

PDE-5 Inhibitor and Intracavernosal Prostaglandin

McMahon and associates[4] reported their results in 93 men with mixed etiology ED who had failed high-dose injection therapy. Thirty-four percent responded to sildenafil alone, 31% responded to combination therapy, and 35% did not respond at all and went on to penile prosthesis or vacuum device or were lost to follow-up. None challenged with intraurethral alprostadil had success. In men on combination therapy, 4 discontinued due to adverse events (severe headache, facial and truncal flushing, penile pain, dyspepsia, and dizziness).

Mydlo and colleagues[5] evaluated the combined use of intracavernosal PGE-1 and oral PDE-5 inhibitors in 34 post nerve-sparing radical prostatectomy patients who had suboptimal response to oral therapy. Eighteen of these men had received 100 mg of sildenafil, and 16 had received 20 mg of vardenafil. These men were subsequently started on 15 or 20 µg of intracavernosal PGE-1. This study did not report the results of combination therapy but did report the effect of injection therapy

on the subsequent development of natural and PDE-5 responsive erectile function. Twenty-two of 32 men who continued therapy reported a significant improvement in erections, and some progressed to minimize the use of intracavernosal injections (ICIs) with sustained response. Thirty-six percent were able to discontinue injections because of the return of “good erections.”

Nandipati and coworkers[6] combined intracavernosal alprostadil and nightly sildenafil in 22 men immediately after nerve-sparing radical prostatectomy. They were instructed to use the injections 2–3 times per week, but the sildenafil was not required to be timed to the injections. The men used injection therapy until natural sexual function returned. At an average follow-up of 6 months, 50% had return of spontaneous partial erections and 96% were sexually active. Of the larger group, 43% used combination therapy and 57% used injections alone. The study was designed to evaluate the role of combination therapy of alprostadil injection and sildenafil on the early return of function. Both of the previous studies suggest a role for combination therapy in penile rehabilitation after prostatectomy.

Gutierrez and associates[7] added intracavernosal PGE-1 injections in a strictly programmed dosage to 40 men with mixed etiology ED who were unsatisfied with their oral sildenafil therapy. The patients received 4 biweekly 20 µg intracavernous PGE-1 injections along with either placebo or 50 mg of sildenafil capsules. Four weeks after initiation of therapy, the 2 groups were crossed over in terms of oral therapy. The authors found a significantly higher satisfaction rate among the group receiving PGE-1 and sildenafil combination compared with those receiving either sildenafil alone or PGE-1 and placebo

4. Safety

The use of the PDE-5 inhibitors in combination with vasoactive compounds is not recommended by the manufacturers within their summary of product characteristics.

As such, it should only be entertained in men with advanced ED that is refractory to oral, intraurethral, or intracavernous therapy. Studies on combination therapy have been done accordingly in men with difficult-to-treat ED. The safety of the combination of sildenafil with intraurethral alprostadil has been demonstrated in several series with a combined total of at least 147 men. The patients were predominantly post prostatectomy or demonstrated vascular disease. All patients received their first combination in the office with 100 mg of sildenafil followed 1 hour later by 500 or 1000 µg of alprostadil. Most patients had already experienced both drugs individually without adverse events. No patients experienced priapism or syncope in any studies.

5. Summary of Key Points for Consideration

National guidance: no national guidance available. No local guidance could be found on the use of combination therapy for erectile dysfunction.

Efficacy

There is currently limited published data supporting the use of combination therapy however what there is appears encouraging. Larger controlled studies are needed to corroborate these encouraging findings.

Rigidity of erection depends on the balance between the production and destruction of cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP), which are constantly being destroyed by phosphodiesterase (PDE) enzymes. PDE- 5 inhibitors block this destruction, whereas alprostadil acts directly on the penile and vascular smooth muscle cells to stimulate production of cAMP.

- Studies have combined intraurethral alprostadil and PDE-5 inhibitors to treat oral monotherapy failures with good results. PDE-5 inhibitors have also been combined with intracavernosal prostaglandins, most often for injection therapy failures, with good results.
- In the published series on combination therapy there have been no cases of priapism, clinical hypotensive episodes, or any serious adverse events, though the total numbers are admittedly small.

Cost:

Current Surrey guidelines support the following:

Treatment with **phosphodiesterase type-5 inhibitors** (sildenafil, tadalafil, vardenafil) at the minimum effective dose is recommended for the groups of patients identified in the Health Service Circular (HSC) 1999/148 at a maximum frequency of dosing of **four** times per month.

OR

Treatment with **prostaglandin E1 intracavernosal injections and intraurethral instillations** are recommended only for the groups of patients identified in the HSC 1999/148 only if oral phosphodiesterase type-5 inhibitors are contraindicated or ineffective at a maximum frequency of dosing of **four** times per month using the drug with the lowest acquisition cost.

If combination therapy was supported there would be a cumulative cost associated with the above recommendation.

5. Conclusions and Recommendations

- Due to the limited evidence currently available to support oral and non-oral combination therapy for erectile dysfunction it is not routinely recommended for use and is considered black on the prescribing advisory database.
- Oral and non-oral combination therapy for erectile dysfunction should be recommended only for the group of patients identified in the HSC 1999/148 with advanced erectile dysfunction only if PDE5 inhibitors and intracavernosal injections / intraurethral instillations are ineffective at a maximum frequency of dosing of **four** times per month using the drug with the lowest acquisition cost

Correspondance
Removed for governance purposes

Appendix 1: References

1. Mydlo JH, Volpe MA, Macchia RJ. Initial results utilizing combination therapy for patients with a suboptimal response to either alprostadil or sildenafil monotherapy. Eur Urol. 2000;38:30–34.
2. Raina R, Nandipati KC, Agarwal A. Combination therapy: medicated urethral system for erection enhances sexual satisfaction in sildenafil citrate failure following nerve-sparing radical prostatectomy. J Androl. 2005;26:757–760
3. Nehra A, Blute ML, Barrett DM, Moreland RB. Rationale for combination therapy of intraurethral prostaglandin E(1) and sildenafil in the salvage of erectile dysfunction patients desiring noninvasive therapy. Int J Impot Res. 2002;14(1 suppl):S38–S42
4. McMahon CG, Samali R, Johnson H. Treatment of intracorporeal injection nonresponse with sildenafil alone or in combination with triple agent intracorporeal injection therapy. J Urol. 1999;162:1992–1997
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6. Nandipati KC, Raina R, Agarwal A, Zippe CD. Early combination therapy: intracavernosal injections and sildenafil following radical prostatectomy increases sexual activity and the return of natural erections. Int J Impot Res. 2006;18:446–451
7. Gutierrez P, Hernandez P, Mas M. Combining programmed intracavernous PGE1 injections and sildenafil on demand to salvage sildenafil nonresponders. Int J Impot Res. 2005;17:354–358