

Considered Judgement Form

This form is a checklist of issues that may be considered by the Purchasing Guidance Advisory Group when making purchasing recommendations.

Meeting date: 24 March 2005

Topic: Evidence based review of medicines for sexual (erectile) dysfunction in men

Background and Purpose:

ACC has a responsibility to support social rehabilitation. In certain circumstances, it therefore funds medicines to treat sexual dysfunction arising directly from physical injury. In such cases, ACC normally funds up to four product treatments per claimant per month. The most common cause of sexual dysfunction in such claimants is spinal cord injury.

A wide range of medicines is now available to treat sexual dysfunction in men (i.e. erectile dysfunction) and some products have been aggressively marketed. ACC's expenditure on such products has increased steadily and substantially over the last 4-5 years.

Sunita Goyal (Pharmaceutical Advisor, Healthwise) has therefore asked the Evidence Based Healthcare Advisory Group to commission a review of the relative effectiveness, cost effectiveness and safety of specified products (see table 1).

Table 1

| Oral medications | Intracavernous self-injection | Intraurethral application | Other |
|---|--|----------------------------------|---|
| PDE5 inhibitors: tadalafil (Cialis [®]), vardenafil (Levitra [®]), and sildenafil (Viagra [®]) Other: sublingual apomorphine (Uprima SL [®]) | Alprostadil (e.g. Caverject [®]), and papaverine (currently the only drug funded by PHARMAC) | Alprostadil (Muse [®]) | Metaraminol (Aramine), used to treat priapism sometimes associated with intracavernous injections |

The aim of the review is to identify a preferred product for the treatment of male ACC claimants experiencing sexual dysfunction as a direct result of physical injury. The review has been carried out by New Zealand Health Technology Assessment (NZHTA), a research unit of the University of Otago.

1. Effectiveness, Volume of Evidence, Applicability /Generalisability and Consistency

Sixteen studies met the criteria for inclusion in the evidence tables (see main report, section 3.1, for a description of the inclusion criteria). Broader criteria were applied to studies focusing on safety, harm or economic factors. Few direct, head to head comparisons of different sexual dysfunction medicines were found in the literature. Most studies looked at general populations with mixed aetiology of sexual dysfunction. Few studies with populations similar to ACC claimants were located. Sildenafil was the only medicine for which eligible studies were available involving this group; these studies dealt with men with spinal cord injury (SCI). The study periods were short for all but those for Silendafil.

On the basis of the efficacy, safety and cost-effectiveness evidence available, the oral PDE5 inhibitor sildenafil (Viagra[®]) appears to be the preferred treatment option for men with erectile dysfunction due to accident or injury. Sildenafil is the longest established and most thoroughly researched PDE5 inhibitor.

While studies on the other PDE5 inhibitors vardenafil (Levitra[®]) and tadalafil (Cialis[®]) suggest acceptable efficacy and safety profiles, and there are some indications of a preference for tadalafil due to its extended period of effectiveness (including Del Popolo et al's crossover trial on 30 men with SCI, published after the literature search for this report had been carried out¹), longer-term efficacy and safety data is not yet available for these agents. With the exception of Del Popolo's study, many trials of these medicines have to date excluded men with SCI.

There is evidence for the efficacy of intracavernous injection therapy with alprostadil, papaverine or combinations of vasoactive agents for those who continue with the treatment. However, trials report significant drop out rates and the evidence is generally at a lower level and from older, poorer quality studies than those focusing on the newer oral PDE5 inhibitors. In addition, a higher incidence of adverse effects is reported in studies of intracavernous injection therapy, particularly with papaverine monotherapy. Although Pharmac-funded in NZ, use of papaverine has been discontinued in many countries due to adverse effects including priapism and penile fibrosis.

Comparative studies have demonstrated greater efficacy for intracavernosal alprostadil (Caverject[®]) than for intraurethral alprostadil (MUSE[®]). The authors suggest that intracavernosal alprostadil be considered in cases where sildenafil is contraindicated or has been ineffective. While there is some evidence for the efficacy of sublingual apomorphine (Uprima SL[®]), it is considered to be less effective than the PDE5 inhibitors and its efficacy has not been demonstrated in men with sexual dysfunction due to SCI.

ACC has in the past funded metaraminol (Aramine) as a treatment for priapism caused by intracavernous injection therapy. However, the authors note that "use of metaraminol has essentially been abandoned due to a reported death from its use". Recent guidelines published by the American Urological Association recommend that priapism be treated by injection of phenylephrine as this agent minimises the risk of cardiovascular side effects².

2. Cost

It was not possible to complete a formal cost effectiveness analysis due to a lack of research and the heterogeneity of the available data. The authors did however make comparisons of average cost per use and reported effectiveness.

The authors conclude that sildenafil is likely to be the most cost-effective option. Tadalafil and vardenafil are on average somewhat less cost effective. In terms of total health dollars, papaverine is also less cost effective than sildenafil but likely to be more so than alprostadil; however, it should be borne in mind that

¹ Del Popolo, G., Marzi, V., Mondaini & Lombardi, G. (2004). Time/duration effectiveness of sildenafil versus tadalafil in the treatment of erectile dysfunction in male spinal cord-injured patients. *Spinal Cord*, 42, 643-648.

² Montague, D. K., Jarow, J., Broderick, G. A., Dmochowski, R. R., Heaton, J. P., Lue, T. F., Nehra, A., et al. (2003). American Urological Association guideline on the management of priapism. *Journal of Urology*, 170, 1318-1324.

papaverine is subsidised by Pharmac. Note also that the cost effectiveness analysis does not take account of potential costs associated with papaverine's increased risk of adverse effects. Intracavernous alprostadil is more cost effective than intraurethral alprostadil. Sublingual apomorphine appears to be the least cost effective treatment option, as it is less efficacious than the similarly priced sildenafil.

The authors note that cost effectiveness decreases with frequency of use and that rationing, particularly of oral medications, may be advisable. They warn that unless limited to ≤ 2 doses per week, sildenafil may be a significantly less cost effective option than intracavernous injection. However, ACC's current policy is to fund no more than 4 product treatments per month unless there are exceptional circumstances.

3. Clinical impact

The authors comment that, compared to self injection and intraurethral treatment, oral medications are far less invasive and easier to administer in men whose motor function may be impaired by injury.

Some men's clinics will offer a cocktail of injectable drugs, with tailored doses for each individual.

4. Equity, Maori/Pacific Health, Acceptability

5. Possible Purchasing Options

ACC already purchases the specified medicines for male sexual dysfunction, where caused by physical injury, as per ACC policy. A proposed order of preference for future purchasing is outlined in section 7.

6. Evidence Statements

Evidence statements:

There is good evidence that sildenafil is an effective treatment for sexual dysfunction generally, and for sexual dysfunction arising directly from physical injury (i.e. SCI).

There is moderate evidence that vardenafil and tadalafil are effective treatments for sexual dysfunction generally. However, apart from one recent study involving tadalafil (see footnote 1 on previous page), their safety and effectiveness for ACC-relevant populations (e.g. SCI patients) have yet to be demonstrated.

There is weaker evidence (i.e. from poorer quality studies) that intracavernous alprostadil is an effective treatment for sexual dysfunction generally. However, significant drop out rates have been reported, and only one small study has demonstrated safety and efficacy in ACC-relevant populations (i.e. SCI patients).

There is some evidence that intraurethral alprostadil and sublingual apomorphine are not as effective as other options for the treatment of sexual dysfunction in men with SCI (sections 4.2 and 4.3.5 respectively).

There is some evidence to suggest that phenylephrine is safer than metaraminol for the treatment of priapism associated with intracavernous injection (section 4.1.7).

7. Purchasing Recommendations

Purchasing recommendations:

1. Purchase sildenafil (Viagra[®]), vardenafil (Levitra[®]) and tadalafil (Cialis[®]) as the first line treatments for male claimants experiencing sexual (erectile) dysfunction arising directly from physical injury.
2. As a second line treatment in cases where sildenafil, vardenafil or tadalafil are contraindicated, or have been ineffective at an appropriate dose over a specified time period, purchase intracavernous alprostadil injection.
3. Except in exceptional circumstances and on advice from the Corporate Medical Advisor, ACC will only

contribute to the cost of a sexual dysfunction medicine in accordance with the dosages and limits for appropriate and safe use as set out in the New Zealand data sheets for the product in question.

Good practice points:

ACC discourages the use of papaverine monotherapy for the treatment of male sexual dysfunction on the grounds that it carries an increased risk of adverse effects.

ACC discourages the use of intraurethral alprostadil and sublingual apomorphine for the treatment of male sexual dysfunction on the grounds that more effective treatment options are now available.

This guidance should be updated in August 2007.

PGAG Discussion

The PGAG requested that some clarity should be given to the term sexual dysfunction when applied to men, and agreed that it should be termed erectile dysfunction as this is the target for these drugs.

There do not appear to large differences in cost between the different drugs included in the review.

Glossary

1. Effectiveness, Volume of Evidence, Applicability /Generalisability and Consistency

Comment here on:

- the extent to which the service/product/ procedure achieves the desired outcomes. Specific reference needs to be made to safety. Report number needed to treat and harm where possible,
- any issues concerning the quantity of evidence and its methodological quality and the extent to which the evidence is directly applicable or generalisable to the New Zealand Population,
- the degree of consistency demonstrated by the available evidence.

Where there are conflicting results, indicate how the group formed a judgement as to the overall direction of the evidence

2. Cost

Comment on:

- any economic costs associated with this service, product or procedure

3. Clinical impact

Comment on:

- the clinical impact eg size of population, magnitude of effect, relative benefit over other management options, resource implications, balance of risk and benefit

4. Equity, Maori/Pacific Health, Acceptability

Comment on the extent to which:

- the service, product or procedure reduces disparities in health status (equity of access, resources, health outcome),
- is consistent with the treaty of Waitangi and encourages Maori/ Pacific participation in providing and using service, product and procedures, and
- is consistent with values and expectations of New Zealanders.

5. Purchasing Options

List the possible purchasing options.

6. Evidence Statement

Summarise the advisory group's synthesis of evidence relating to this service, product or procedure, taking the above factors into account, and indicate the evidence level that applies.

7. Recommendations

What recommendation(s) does the advisory group draw from this evidence?