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Polycystic ovary syndrome

Hormone replacement therapy

Combined oral contraceptives

Erectile dysfunction

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The dilemma of practicing evidence based medicine when it keeps changing

Suicide and antidepressants

It's 2002; An 18-year old male patient, suffering from depression and anxiety is seeking treatment. You prescribe him what evidence shows to be a safe and effective antidepressant—paroxetine.

Fast forward to 2008; does evidence suggest you prescribe this drug now? SSRIs have gone from being widely popular to being associated with suicide risk, and then used again as the level of risk was outweighed by untreated depression. Now a recent study claims that they do not work at all. The story is sure to continue.

The rate of antidepressant prescriptions in children and adolescents was steadily rising until 2003 when worldwide regulatory agencies issued public health advice ("black box warnings") in response to reports that young people starting antidepressants, especially SSRIs, were experiencing sudden onset of agitation and suicidal thoughts.[1] After the warnings were issued, antidepressant prescribing reduced considerably and some mental health professionals expressed concern that this may result in increased levels of untreated depression and subsequent suicide.

Conflicting evidence of an increase in youth suicides

Since the black box warnings, there have been two major observational studies published which investigated the possible association between antidepressant prescriptions and completed suicide or suicidal behaviour. These studies reached conflicting conclusions.

Researchers from the USA and Netherlands studied national health records to identify suicide rates, before and after the public health warnings were issued. In the Netherlands, the youth suicide rate increased by 49% between 2003 and 2005 and was significantly associated with the decline in SSRI prescriptions. The most significant association was for boys under 15 years. In the USA, the youth suicide rate increased by 14% between 2003 and 2004, which was the largest yearly change recorded since 1979. Prior to the warnings, SSRI prescription rates were increasing and suicide rates were decreasing in both countries.[2]

Data from a recently released ecological time series study from the UK, using national prescribing, mortality

and hospitalisation data, contradicts these results. Researchers found no evidence of an association between trends in antidepressant prescribing and suicide or hospital admissions for self harm, despite a large reduction in antidepressant prescribing since the warnings in 2003. There were no obvious differences between the populations in either study that would explain this discrepancy.[3]

While causal associations drawn from ecological studies are often difficult to prove, the results of these studies raise some important questions about the validity of the original black box warnings for SSRIs and perhaps more importantly, whether antidepressants actually work for young people with depression.

Was the black box warning valid?

It appears now that the black box warning was a reaction to weak evidence, which had serious consequences if true. There have been no observations of completed suicides in any of the SSRI trials to date.

There is a higher risk of suicide in real populations compared to study populations. In the trials, the rate of suicide related behaviours was 5% for people using SSRIs and 3% for people using placebo.[4] Community studies show that over a fifth of young people report serious suicidal ideation and around 7% report suicide attempts.[5] In most trials of medication, those at risk of suicide are typically screened out. So the population on which the trials have been done are at particularly low risk of suicide related behaviours and so are not those typically seen in clinical practice.

In addition, the studies were not set up to assess suicide risk and were not powered to do this. The ways in which suicide related behaviours were assessed varied from study to study. In the Treatment of Adolescents with Depression (TADS) study, a self-report measure of suicidal ideation was used and this showed a steady drop in suicide risk while on antidepressant medication.[6]

Are antidepressants effective treatments for depressive disorder in children and adolescents?

The evidence is inconclusive at this stage. Tricyclic antidepressants are not effective for children and adolescents with depression[7] and there is limited evidence that SSRIs other than fluoxetine have anything more than a placebo response.[8, 9] Even for fluoxetine the overall response rate is low.[10]

It is unclear whether long-term use of antidepressants in children results in adverse effects. Some studies suggest that children taking long-term antidepressants are at increased risk of developing bipolar disorder and other neurological effects.[1] Psychological therapies are recommended as first-line treatment for this age group.[11]

Changing evidence

The example of the antidepressants "story" demonstrates the complexity of trying to practice evidence based medicine when it keeps changing. In this case, the implicit consequence of the evidence, if proven true, has been the main influence on the cycle of treatment.

What we know now is that antidepressants are unlikely to increase suicidal behaviour in young people, but there is doubt over whether they work at all.

A 2005 study found that 16% of top-cited clinical research articles on medical interventions published in the last fifteen years have been contradicted by subsequent clinical studies. In addition, a further 16% of research was found to have initially stronger effects than later research found.[12] This is a worrying statistic for those who strive to practice evidence based medicine.

There is a huge volume of research published in medical journals each year but only a small minority of papers receive attention and dominate scientific thought and practice. Original highly cited articles are published almost

exclusively in three general medical journals – the New England Journal of Medicine, the Journal of the American Medical Association (JAMA) and Lancet.[12]

High impact research may be further influenced by several biases. "Publication bias" and "time lag bias" favour rapid and prominent publication of positive findings.[12] "Wish bias" is when researchers are selective in the results they choose to publish or the research they choose to refute due to their desire for their own beliefs to be true.[13]

The strength of a study's findings should be measured by the amount of supporting research. Observational studies are often contradicted by randomised controlled trials and small studies are contradicted by studies with much larger sample sizes.[12]

There are several reasons why researchers may get it wrong.

- Statistical significance is not always equal to clinical significance. Level of significance is arbitrary; traditionally a P value of <0.05 is considered significant, however significance should be interpreted in the context of the study.
- Initially stronger effects may be due to chance variability.
- Evidence from a unique trial may be refuted with subsequent study in the area.
- Studies may not be able to be replicated and therefore results cannot be confirmed.

There is no proof that subsequent contradictory studies are themselves true. However the overall effect is that it generates uncertainty for clinical practice.[12] In the course of developing both the HRT and antidepressant articles for this edition of best practice, evidence changed and advice had to be updated.

Trying to make sense of research evidence can be complex and time consuming and as seen here, even the experts get it wrong. It is often unavoidable to follow latest evidence, especially when it receives much media attention. However wherever possible, an informed but pragmatic approach is "best practice".

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Understanding polycystic ovary syndrome

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Key messages:

- Polycystic ovary syndrome (PCOS) is associated with a range of metabolic abnormalities which can lead to long term health problems
- PCOS is the most common endocrine disorder among young women
- PCOS is a syndrome so there is not a single diagnostic test
- Lifestyle changes play an important role in management of the syndrome
- Management should be individually tailored for each patient depending on the type of symptoms and clinical features found

Background

PCOS is characterised by a varied and often complex array of metabolic and endocrine abnormalities. The syndrome was originally described by Stein and Leventhal in 1935, as a triad consisting of amennorhoea, hirsutism and obesity, in women who had multiple cysts on their ovaries.[1] Over the last decade or so, the understanding of this syndrome has changed and the emphasis is often on the long-term consequences that may occur.

Prevalence of PCOS

PCOS is the most common endocrine disorder among young women. Accurate prevalence figures are hard to find because of the lack of consensus that has existed regarding diagnosis,[2] however it is reported to affect between 5-10% of women of reproductive age.[2, 3] New Zealand studies report a similar proportion of women with PCOS although the ultrasound finding of polycystic ovaries is considerably more common, being found in 21% of randomly selected New Zealand women.[4] PCOS is also often undiagnosed.[5]

Cause of PCOS not fully understood

The pathogenesis of PCOS is not fully understood.[6] There is some evidence of a polygenic component.[7, 8] Insulin resistance is an important element in the development of PCOS but there are complex interactions involving many systems (Figure 1).

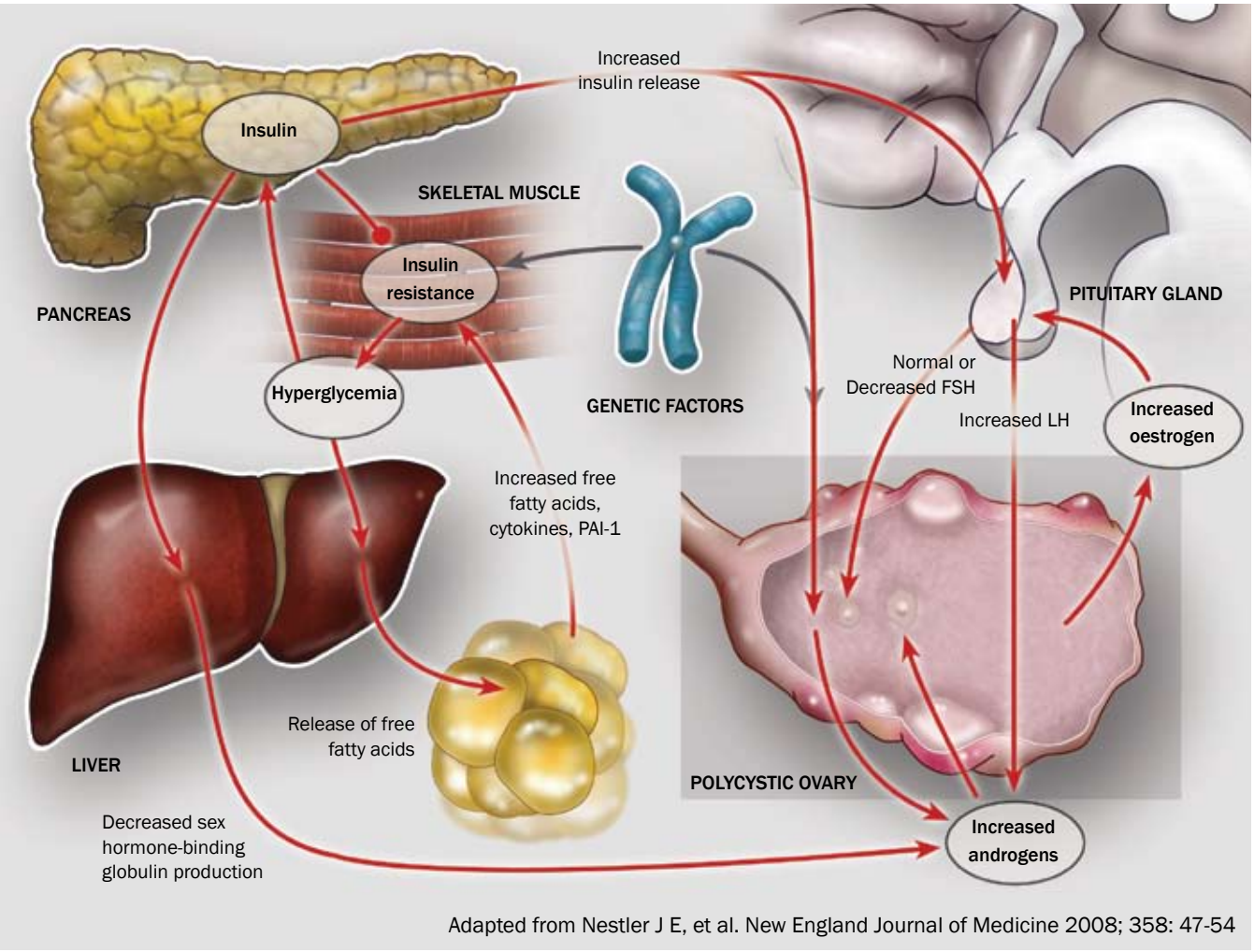

Figure 1: Pathophysiological characteristics of PCOS. This figure illustrates the complex interactions underlying the pathophysiology of PCOS. Insulin resistance and the resulting hyperinsulinemia are responsible for the majority of the changes found in PCOS.

Long term health risks in PCOS

It is generally accepted that women with PCOS are at increased risk of:

- Impaired glucose tolerance, metabolic syndrome, gestational diabetes and type 2 diabetes[9]
- Hypertension, dyslipidaemia and cardiovascular disease[10]
- Fertility problems
- Endometrial hyperplasia and therefore endometrial cancer[11, 12]

Recent studies have shown an increased risk of obstructive sleep apnoea, irrespective of BMI.[12] An association between PCOS and breast and ovarian cancers has also been suggested but the evidence is conflicting.[11, 13]

Studies have identified that insulin resistance appears to be responsible for many of these long term health consequences.[8, 14] Obesity contributes to the risks, but not all women with PCOS are obese. Hyperinsulinaemia and other metabolic changes are present even in lean women with PCOS.[11]

There are, however, other factors often present in women with PCOS that may also contribute to these health risks. For example, unopposed oestrogens are a risk factor for endometrial hyperplasia and carcinoma. In addition, both

diabetes and obesity have been linked to an increased risk of endometrial carcinoma.

A woman with PCOS therefore may have many factors that could increase her long term health risks and it has been difficult so far to determine the exact roles of each factor.[13]

Diagnosing PCOS

Diagnostic criteria have been developed for PCOS

PCOS is a syndrome, so there is no single diagnostic test. Diagnostic criteria have been developed (Box 1) and widely adopted internationally. However, diagnosis can be difficult due to the variation in presenting symptoms and because symptoms differ with age at presentation and change over time.

Presenting features of PCOS

Although presenting features (Box 2), age of presentation and severity of PCOS vary, a common presentation may be of a woman with a history of gradually worsening hirsutism and irregular periods, which goes back for some years. For many women however, failure to conceive may be the initial reason for presentation.

A full history is needed

It is important when taking the history to include questions about:

- Reproductive health (menarche, past and present cycle, oligo-/amenorrhoea, menorrhagia, miscarriage, infertility)
- Presence of androgenic symptoms (acne, hirsutism, alopecia of the scalp)
- Lifestyle factors (changes in body weight, eating and exercise habits, alcohol and smoking history)
- Family history of PCOS, diabetes, obesity, hirsutism and premature male baldness.[13]

Box 1: Rotterdam Consensus on Diagnostic Criteria for PCOS[9]

Two out of three of the following:

1. Oligo- or anovulation
2. Clinical and/or biochemical signs of hyperandrogenism*
3. Polycystic ovaries**

and exclusion of other etiologies (congenital adrenal hyperplasia, androgen-secreting tumours, Cushing's syndrome)

* Hirsutism, acne, male pattern baldness, elevated total or free testosterone

** On ultrasound, ≥12 follicles of 2-9mm diameter and/or increased ovarian volume (>10mL)

Box 2: Presenting features of PCOS[5, 8, 13, 14]

Presenting features (% affected)

- Hyperandrogenism (hirsutism 70%, acne 30%, alopecia 10%, but not virilisation*)
- Menstrual disturbance 60-70%
- Infertility 70%
- Obesity, particularly truncal 35-50%
- Polycystic ovaries visible on ultrasound in asymptomatic woman 22-33%
- Acanthosis nigricans 1-3% **

* Rapid development of virilisation signals a need for investigation to rule out the presence of an androgen secreting tumour.[8, 15]

** A brown-discoloured 'velvety' texture to the skin typically in the region of the axillae and the back of the neck, often considered to be the cutaneous manifestation of insulin resistance (or hyperinsulinaemia).

Examination includes general as well as reproductive features

Examination of a woman with suspected PCOS should include an assessment of:

- Weight (both BMI and hip/waist ratio)
- Acne and hirsutism
- Blood pressure

Additional examination depending on the presenting features may include breast, abdominal and pelvic exam. The presence of abdominal striae could indicate weight change or Cushing's syndrome. A bimanual examination may identify ovarian enlargement, although clinical pelvic examination is a poor predictor of polycystic ovaries, especially if the BMI is high. The presence of features of virilisation (which may include frontal balding, deepening of the voice, broadening of the shoulders, breast atrophy, clitoromegaly and loss of vaginal rugae) may raise concerns about other serious conditions.[13]

Investigation of PCOS

A clinical or biochemical finding of increased androgen levels along with either menstrual abnormalities or polycystic ovaries on ultrasound will satisfy the current diagnostic criteria (Box 1). The initial tests recommended for diagnosis are outlined in Table 1. While not essential

Table 1: Recommended investigations for aiding diagnosis of PCOS

Investigation	Expected finding in PCOS	Comment
Recommended investigations for diagnosis		
Exclude pregnancy		Most common cause of amenorrhoea.[13, 14]
Pelvic ultrasound	Polycystic ovaries	Important as part of the diagnostic criteria but not a "must do" if diagnosis is made on clinical and biochemical grounds.
Free testosterone	Usually increased	More sensitive for identifying physiologically active androgens. This is calculated from total testosterone and SHBG. Very high levels of total testosterone require further investigation to rule out other causes such as late-onset congenital adrenal hyperplasia, Cushing's syndrome, adrenal or ovarian tumour. SHBG levels are decreased in PCOS.
Recommended investigations after diagnosis		
Glucose		To check for glucose intolerance or diabetes. If fasting level > 5.5 mmol/L or random > 7.7 mmol/L then a glucose tolerance test is recommended.
Lipids	Usually high triglycerides, lower HDL and mildly elevated LDL.[11]	A fasting level may be useful in establishing cardiovascular risk.
Other tests to consider		
LH/FSH	LH will often be increased, FSH usually normal, giving an increased ratio	While not essential for diagnosis, some clinicians remain convinced of the value of LH testing in predicting future complications of PCOS.

Table 2: Tests to exclude other conditions (depending on clinical suspicion)

Test	Reason	Clinical signs
Prolactin	Very high levels may suggest a pituitary cause or medication use (especially antipsychotic medication)	Galactorrhoea Irregular or absent periods
TSH	To exclude thyroid abnormalities as a cause of menstrual irregularity[14]	Menstrual changes associated with other thyroid symptoms (either hypo or hyper)
Oestradiol + FSH	To help exclude premature ovarian failure (low oestradiol, very high FSH)[7]	Menopausal symptoms and signs in women less than 40 years
17-OH progesterone	To help exclude late-onset or non-classic congenital adrenal hyperplasia (very rare)	Difficult to distinguish clinically from PCOS. However there may be a family history of CAH, less menstrual disruption or history of early growth of pubic hair.
DHEAS	A marker for adrenal androgen production, very high levels may be associated with an adrenocortical tumour[15]	Rapid onset of virilising features
Androstenedione	A marker for ovarian androgen production, very high levels may be associated with an ovarian androgen secreting tumour[15]	Rapid onset of virilising features
24hr urine cortisol	Increased in Cushing's syndrome	Typical Cushingoid features e.g. central obesity, moon face, thinning of skin, striae, excessive sweating

for diagnosis, some clinicians still suggest testing LH/FSH. Once the diagnosis is established, fasting glucose and lipids are recommended. Other tests may be required depending on clinical suspicion, to exclude other conditions (Table 2).

Treatment and management of PCOS

Lifestyle modification to reduce weight is the most effective first line treatment in PCOS.[14, 16, 17] Even a modest weight loss of 5% will reduce central obesity and insulin resistance and improve endocrinological abnormalities and menstrual irregularity (including increasing the rate of ovulation).[17] Ultimately, women who succeed in losing weight are more likely to achieve and have a healthier pregnancy and reduce their risk of gestational diabetes. Longer term benefits of weight loss result from the reduction in insulin resistance. Note that weight loss is not necessary if BMI is within normal range.

Changes in serum endocrinology in PCOS[8]

There are multiple biochemical changes in women with PCOS. The key feature is the increased level of serum androgens which are responsible for most of the common presenting features:

- Increased androgens (testosterone, androstenedione and dehydro-epiandrosterone sulphate (DHEAS))
- Increased luteinising hormone (LH)
- Decreased sex hormone binding globulin (SHBG)
- Increased prolactin
- Increased oestradiol
- Increased insulin

Do not test insulin

Fasting serum insulin is a poor measure of insulin resistance.[18] Although used widely in large population-based epidemiological studies, it is not recommended for use in a general practice setting. It is more useful to identify the risk factors that are associated with insulin resistance (and often therefore identify metabolic syndrome and PCOS). These risk factors include raised fasting glucose and lipid levels, high blood pressure and central obesity.

Ethnicity and PCOS

Limited data exist on prevalence between different ethnic groups in New Zealand. A cross-sectional study of women presenting to the gynae-endocrine clinic at National Women's Hospital who were diagnosed with PCOS showed rates for European, Māori and Pacific Island women in proportion to the general population. Although numbers were small, Indian women appeared to be over-represented and Chinese women under-represented.

What may be more important though is that Māori and Pacific Island women with PCOS were more likely to be obese and had significantly more adverse metabolic features, higher levels of androgens, triglycerides, LDL cholesterol, fasting insulin, systolic and diastolic blood pressure, and lower HDL.[19]

Treatment may be required for acne and hirsutism, which are often the major reasons for women to present. Treatment options may include anti-androgens, topical agents (particularly for acne) and local hirsutism treatments (including electrolysis and laser therapy). The combination of acne, hirsutism and obesity is likely to lower self esteem in women with PCOS. Psychological support may be required and this may also help women achieve the recommended beneficial lifestyle changes.

First line anti-androgenic therapy is often in the form of a combined oral contraceptive pill containing cyproterone acetate, and/or the diuretic spironolactone (usually 100–200 mg/day), which has an anti-androgenic effect. As a second line treatment, higher dose regimens of cyproterone acetate or spironolactone may be combined with oral contraceptive pill use.

Regulation of the menstrual cycle may be achieved with weight loss, a combined oral contraceptive or progesterone therapy (if COC not tolerated). Most clinicians would currently recommend the use of these hormonal treatments to protect the endometrium from unopposed oestrogen stimulation in women who have chronic anovulation.[11, 14]

Metformin, which is an insulin sensitising agent, has been advocated as a treatment for PCOS. Theoretically it should decrease insulin levels and therefore reduce androgen production, and help restore the endocrinological abnormalities of PCOS. It has been suggested that it may aid weight loss, but there is currently no evidence to support this.[14]

There is ongoing debate regarding the appropriateness of metformin as first choice treatment in women with PCOS who are having fertility problems. It appears that in many studies metformin results in no improvement in live birth rates compared to clomiphene citrate.[18, 20] A multi-centre New Zealand randomised trial PCOSMIC (PCOS Metformin for Infertility with Clomiphene) will help to define the place of metformin in ovulation induction and is expected to be completed in 2008.[21]

If infertility is the main presenting problem, specialist referral is recommended. Clomiphene citrate is considered first line treatment.[14, 22] To avoid the risk of over-response leading to multiple pregnancy, clomiphene citrate treatment is carefully monitored through a fertility clinic (with late follicular serum oestradiol levels and ultrasound scanning

when appropriate). Weight reduction, if appropriate, remains central to the success of any treatment.

Ongoing preventive screening of cardiovascular and endometrial disease risk factors is important when managing women with PCOS. There are no consensus guidelines in widespread use. A sensible approach would be to check BMI and blood pressure annually, along with fasting lipids and a glucose tolerance test every three to five years in patients with low cardiovascular risk, or every one to three years where other risk factors, such as obesity, are present.

These consultations give women with PCOS the opportunity to review lifestyle factors to optimise their long term health. For women with anovulation who elect not to use endometrial protection, regular screening by transvaginal ultrasound and/or endometrial biopsy every one to two years is advisable.

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Hormone replacement therapy: latest evidence and treatment recommendations

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Summary

- HRT is indicated for the treatment of moderate to severe vasomotor and urogenital symptoms associated with menopause.
- HRT is not recommended for primary prevention of disease because of increased risk of other adverse events.
- The use of HRT increases the risk of stroke, venous thromboembolism (VTE) and gall bladder disease and combined oestrogen progestogen therapy is also associated with an increased risk of breast cancer and dementia (women >65).
- Individual risk assessment is essential before starting HRT therapy. For women younger than 50, or those at low risk of cardiovascular disease, stroke, or breast cancer, the absolute risk from HRT is likely to be small.
- HRT should be prescribed at the lowest effective dose for the shortest duration possible. Other treatments should also be considered. Regular monitoring is necessary, along with attempted withdrawal after one to two years.

Definitions

HRT	Hormone replacement therapy (oestrogen only or combined therapy)
Oestrogen therapy	Oestrogen only
Combined therapy	Oestrogen + progestogen
Continuous combined therapy	Oestrogen + progestogen administered daily
Continuous sequential therapy	Oestrogen daily + progestogen (10–14 days each month)
Progestogen	Progesterone or progestin
Perimenopause	Period of approximately three to six years during which menstrual cycles become erratic and oestrogen levels fall, ending with the cessation of menstruation
Postmenopause	One year without menstruation

Treatment and management recommendations

Although most women manage menopause themselves, around 10% seek help from a GP or specialist.[1] Hormone replacement therapy (HRT) was very popular until 2002 when evidence began to emerge of significant risks. However, HRT remains the most effective treatment for symptoms of menopause and may be used with minimal risk by some women.

Risk-benefit assessment

When deciding whether to prescribe HRT, first consider treatment goals, benefits and risks for the individual woman.[2] HRT improves quality of life in women experiencing moderate to severe menopausal symptoms.

Factors to consider;[2]

- Time of menopause
- Impact of symptoms on quality of life
- Underlying risk of CVD, stroke, VTE, cancers and other conditions
- Suitability of other treatments

The decision to treat is based on what level of individual risk (and benefit) is acceptable to both patient and doctor.

Table 1 (over page) summarises the risks and benefits associated with HRT use.

Contraindications for HRT

HRT should not be used for women with the following risk factors:

- Previous breast cancer
- Previous or high risk of cardiovascular disease
- Previous or high risk of VTE
- Dementia

HRT is not recommended for prevention of chronic illness.

Indications for HRT

Adapted from "Managing the menopause", Dr Helen Roberts (2007).[1]

The primary indications for HRT are **hot flushes, night sweats** and **urogenital symptoms.** The patient's perception of severity of their symptoms should guide treatment, not hormone levels as they tend to fluctuate throughout peri-menopause. There is little evidence that **mood symptoms** are worsened during menopause and this is not an indication alone for HRT therapy.

Improvements in **hot flush** and **night sweat** symptoms may be seen within four weeks of beginning therapy. Short term use of HRT (one to two years) is appropriate as flushes disappear within a few years of menopause in about two thirds of women.

Urogenital symptoms, e.g. dryness, soreness, dyspareunia (painful sexual intercourse) and increased urinary frequency and urgency, occur in around 50% of women after menopause. Topical vaginal oestrogen may provide benefit in dyspareunia and decrease recurrent UTIs in susceptible women. Response can take several months and longer term treatment is often needed. Systemic absorption is minimal so the risks from oral oestrogen do not apply and concurrent progestogen is not required for women with a uterus.

Management and dosing regimens for HRT

There are no specific data on individual forms of HRT and whether their safety profile differs. Most of the major trials have tested conjugated equine oestrogens alone or with medroxyyprogesterone acetate. Recommended treatment regimens are listed in Table 2 (over page)

Women with **premature menopause** may have more severe symptoms, requiring higher doses of HRT.

Adverse effects of HRT include irregular bleeding with combined regimens, nausea and breast tenderness. These symptoms usually decrease over time, but lowering the dose of the hormones may reduce these effects.

Table 1: Summary of risks and benefits of HRT

	Risks	Benefits
Combined treatment (oestrogen plus progestogen)	Breast cancer Coronary heart disease (first year of use) Dementia and cognition (>65 years) Gallbladder disease Stroke VTE ? Ovarian cancer	Vasomotor symptoms e.g. hot flushes Urogenital symptoms e.g. dryness Sleep disturbances Osteoporotic fracture Colorectal cancer ? Diabetes
Oestrogen only treatment	Endometrial cancer (if uterus present) Gallbladder disease Stroke VTE ? Ovarian cancer	Vasomotor symptoms e.g. hot flushes Urogenital symptoms e.g. dryness Sleep disturbances Osteoporotic fracture Colorectal cancer ? Depression ? Diabetes

Table 2: Recommended treatment regimens

"Use the lowest effective dose, for the shortest duration possible"

Women beginning treatment	0.3 mg conjugated equine oestrogen or 0.5 – 1.0 mg 17-β-oestradiol or oestradiol valerate (low dose). Doses can be increased after a few weeks if symptom relief is not adequate.
Women who have had a hysterectomy	Oestrogen only
Women with a uterus	Add progestogen to protect endometrium (tablets or intrauterine system). Low dose prepacked regimens can be used initially (e.g. Kliovance), or progestogen doses can be extrapolated from these regimens and progestogen only pills containing norethisterone or levonorgestrel can be used. The intrauterine system (Mirena) may be a good option for perimenopausal women as it also offers contraception.
Perimenopausal or recent menopause	Combined sequential treatment (oestrogen daily with progestogen 10 – 14 days per month). For women still menstruating, oestrogen should be started on the first day of menstrual bleed and progestogen given 14 days later, withdrawal bleeding should then start at the time that the next period would be expected.
Postmenopausal for greater than one year (over two years since last menstrual period)	Combined continuous treatment (oestrogen and progestogen daily). May cause irregular bleeding in first 6 – 12 months of use.

Monitoring and investigation

Before beginning treatment with HRT, evaluation includes a cardiovascular risk assessment and up to date breast and cervical screening. Referral for bone densitometry is determined on a case by case basis.[2] Endometrial investigation (ultrasound) is not normally required unless there has been bleeding between periods or bleeding after one year with no periods.[1]

After treatment with HRT has commenced, review regularly based on individual need. Blood pressure measurement is recommended at each review. Other investigations should be done as indicated. Cervical smears should be performed based on national screening recommendations and mammograms performed every two years from age 45 to 69.[3]

How to discontinue HRT

Approximately 75% of women stop HRT within two years, usually without seeing their doctor. Attempted withdrawal is appropriate after one or two years, to see if symptoms have resolved.[1] Symptoms have an approximately 50% chance off reoccurring if treatment is stopped, regardless of age, length of treatment or method of withdrawal.[2]

Experts are divided in their opinion on whether HRT should be abruptly withdrawn or slowly tapered; women can be given the choice.

Dr Helen Roberts offers a best practice tip: If after a trial withdrawal, the patient experiences a severe return of symptoms, then HRT could be restarted but the dose slowly decreased over the next three to six months. Non-hormonal treatments could also be added that help flushes. Women with long term debilitating symptoms will need to balance symptom relief with ongoing risks from therapy.[1]

Alternatives to HRT

Life style factors such as stress reduction, regular exercise, weight management, diet, avoidance of smoking, excessive caffeine and alcohol intake can be helpful.[1, 3]

Other medications that may be effective for mild menopausal symptoms, include SSRIs (fluoxetine, paroxetine and venlafaxine have all shown benefit in reducing hot flushes) and clonidine.[1,3]

Tibolone is a synthetic steroid with weak oestrogenic, progestogenic and androgenic effects. It may be used as an alternative to HRT for women more than 12 months post menopause for the treatment of hot flushes and vaginal dryness. Randomised controlled trials show that tibolone is not associated with any change in mammographic density or any increased risk of VTE. The risk of breast cancer, stroke and cardiovascular disease is thought to be similar to standard hormone treatment.[1, 3] Tibolone is registered for use in New Zealand but currently not available.

Alternative therapies are commonly used to treat menopause symptoms. A large scale systematic review concluded that although individual trials suggest possible benefit of some products, overall there is no evidence to suggest that any alternative therapies are effective for treating the symptoms of menopause.[4] Use of alternative products is an individual choice and may be appropriate in women for whom HRT is contraindicated or not tolerated.

Evidence shows that soy products, dong quai, evening primrose oil, red clover, black cohosh and ginseng have no significant impact on hot flushes or sleep disturbances.[4, 5]

Transdermal wild yam creams are promoted as a natural source of progesterone. They contain diosgenin, a steroid with no hormonal activity, which can be synthesised into progesterone in a laboratory setting. However the human body is unable to do this. Wild yam cream appears to have little effect on menopause symptoms and should not be used in place of progestogen treatment.[6]

Progesterone creams have limited evidence of effectiveness. There is no assurance that these creams would provide adequate protection of the endometrium for women using oestrogen, therefore they are not recommended in place of other forms of progestogen.[1]

Evidence of risks and benefits

** Hazard ratios for women aged 50 – 79 using HRT, calculated based on results from the WHI study.[1] A hazard ratio of 1.25 would mean that risk is increased by a further 25% of baseline risk e.g. baseline risk = 5%, hazard ratio for treatment = 1.25, therefore new risk = 5 x 1.25 = 6.25%. It is important to interpret risk in relation to baseline risk, which can vary with the individual.*

Risks and benefits of HRT for specific outcomes

Osteoporosis: There is strong evidence that HRT is beneficial in reducing the risk of postmenopausal osteoporotic fracture and increasing bone density.[2] Although some evidence suggests that a few years treatment around the time of menopause can be beneficial in fracture reduction,[7] it is generally agreed that life long use of HRT is required to prevent bone fractures. HRT is however not first line treatment for women with low bone mineral density due to the increased risk of other negative outcomes.

Hazard ratio for increased risk of fracture (95% CI): Combined treatment 0.76 (0.69 – 0.85). Oestrogen only treatment 0.70 (0.63 – 0.79).

Coronary Heart Disease: There is conflicting evidence of the effect of HRT on cardiovascular risk. The timing hypothesis may explain this conflict. It theorises that oestrogen in recently menopausal women could prevent the development of coronary artery plaque but would have no effect, or even cause harm if given to older women with compromised plaque.[8]

The Women's Health Initiative trial (WHI) found an overall increase in coronary heart disease in the first year of use of combined HRT.[9] However, overall a non-significant reduction in the risk of coronary heart disease was observed in women aged 50–59 years (oestrogen only trial) and in women for whom menopause had occurred within the previous ten years (combined trial).[10]

An increased risk of cardiac events was observed in the Women's International Study of Long Duration Oestrogen (WISDOM), in women using combined treatment. However, most of these women were over 64 years at trial entry and had one or more cardiovascular risk factors.[11]

Hazard ratio for increased risk of coronary heart disease (95% CI): Combined treatment overall 1.24 (1.00 – 1.54), first year of use 1.81(1.09-3.01). Oestrogen only treatment 0.95 (0.70 – 1.16).

Stroke: An increased rate of stroke was observed in the WHI study, with both combined treatment and oestrogen only treatment. The absolute risk of stroke was lower for women under 60 or in whom menopause had occurred within the previous five years.[2]

Hazard ratio for increased risk of ischaemic stroke (95% CI): Combined treatment 1.41 (1.07 – 1.85). Oestrogen only treatment 1.39 (1.10 – 1.77).

Dementia: HRT does not prevent cognitive decline in older postmenopausal women.[12] There is some evidence that HRT may increase the risk of dementia when given to women over 65 years of age.[2] A beneficial effect on cognition has been observed when HRT is used in younger women, however evidence is inconsistent. In the WHI study, a two-fold increase in dementia was found in women over 75 years taking HRT.[7]

Hazard ratio for increased risk of dementia (>65 years) (95% CI): Combined treatment 2.05 (1.21 –3.48). Oestrogen only treatment 1.49 (0.83 – 2.66).

Ovarian cancer: Although evidence is conflicting, it has been concluded that HRT, especially oestrogen only therapy is associated with an increased risk of ovarian cancer.[13, 14] A meta analysis found that the risk was increased by 1.28 with oestrogen therapy and 1.11 with combined therapy.[14]

Venous thromboembolism (VTE): a significant increase in the risk of VTE has been observed in post menopausal women using HRT. The risk appears to be greatest during the first one to two years of treatment and decreases over time.[2, 7] Although HRT increases the risk of VTE up to two-fold, the absolute risk is small, with a baseline risk of 1.7 events per 1000 women over 50 not taking HRT.[7]

Younger age, lower HRT doses, transdermal HRT and oestrogen treatment alone may also be associated with less risk.[2, 5, 7] Women who have previously suffered a VTE event have an increased risk of recurrence in the first year of HRT use.[7] Older age, obesity and underlying thrombotic disorders also significantly increase risk.[2]

Hazard ratio for increased risk of DVT (95% CI): Combined treatment 1.95 (1.43 – 2.67). Oestrogen only treatment 1.47 (1.06 – 2.06).

Breast cancer: Combined treatment with oestrogen and progestogen increases the risk of breast cancer diagnosis or recurrence. Oestrogen treatment alone does not appear to increase this risk. The greatest risk is with use of combined treatment for more than five years, when treatment is started over 50 years of age, increasing with duration of use. It is not known if the risk is different for continuous or sequential use of progestogen.[2, 5, 7]

In the WHI study, an increase in invasive cancers was observed in women using combined treatment for five or more years and a non-statistically significant decrease in those using oestrogen alone, after an average of 7.1 years. There is limited observational data that oestrogen use for more than 15 years may be associated with increased risk of breast cancer.[2]

Combined HRT treatment and to a lesser extent, oestrogen only treatment, increases breast cell proliferation, breast pain and mammographic density and may impede the diagnostic interpretation of mammograms.[2]

Hazard ratio for increased risk of breast cancer (95% CI): Combined treatment 1.24 (1.01 – 1.54). Oestrogen only treatment 0.77 (0.59 – 1.01).

Summary

HRT is associated with the greatest risk when it is taken for more than five years, in women over 60 years of age. However the highest risk of VTE occurs within the first year of treatment. Short term HRT is appropriate in a healthy woman, within five years of menopause, experiencing moderate to severe symptoms. Careful consideration should be given to using HRT for more than five years or in women with risk factors for other conditions.

Useful website:

The US National Institutes of Health website is a good resource for HRT information.

http://health.nih.gov/result.asp/961

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Combined oral contraceptive: **Issues for current users**

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Approximately 147,000 women in New Zealand take oral contraceptives. About 80% of these women take combined oral contraceptives (COC) containing oestrogen and a progestogen.[1]

This article offers guidance for managing situations when women who are currently using COCs:

- Develop conditions which affect their suitability for COC use.
- Require other medicines that interact with COCs.
- Experience adverse effects.

A follow up visit is appropriate to measure blood pressure and assess any problems, three months after a first prescription of an oral contraceptive, and then at least yearly thereafter. Women should also be advised to return if any problems arise.[2]

Medical conditions that affect the suitability of COC use

The use of COCs must be carefully considered in certain medical conditions. The UK Medical Eligibility Criteria (UKMEC) for combined oral contraceptive use provides guidance on suitability of COCs in particular conditions (pages 28–29).[2]

Conditions that may require review of COC use

Women whose clinical condition changes while using hormonal contraception require assessment on an individual basis. It may be appropriate to discuss risks and benefits and offer alternative contraceptive methods that pose less risk.

COCs are contraindicated in migraine with aura

Combined oral contraceptives increase the risk of stroke in women who suffer from migraines with aura. COC's should therefore not be started by women of any age who suffer from migraine with aura. They should also be discontinued in women who develop migraine with aura whilst already on COC.[3] Progestogen only or non hormonal methods can be considered for these women.[3]

COCs are best discontinued if migraine without aura develops

It is usually recommended that women who develop migraine without aura following initiation of COC should discontinue use, especially women over 35 years. Progestogen only or non hormonal methods can also be considered for these women.[3]

Pre-existing migraine without aura in women less than 35 years old is not a contraindication to COC initiation.

COCs increase the risk of venous thromboembolism

Combined oral contraceptive users have a higher risk of venous thromboembolism (VTE) than non-users (see side bar).

COCs are contraindicated for women with a current or past history of VTE and best avoided for those at high risk. Risk factors include obesity, smoking, or a family history of VTE in a first degree relative younger than 45 years old.[3] Progestogen only or non hormonal methods can be used.

COC use in heavy smokers substantially increases cardiovascular risk.[3]

COCs can generally be used in women younger than 35 years who smoke, however their use is not advised in women over 35 years who smoke. Progestogen only or non hormonal methods can be used in women who smoke.

Progestogen Only Pills (POPs)

POPs available in New Zealand contain; levonorgestrel, norethisterone or desogestrel. POPs mainly work by their action on the cervical mucous, however Cerazette is different in that the mode of action is ovulation inhibition. They have less contraindications to use compared with COCs however they require much more rigid compliance and have to be taken at the same time every day (within three hours, or within 12 hours for Cerazette). Breakthrough bleeding or spotting is more common with POP use than with COCs. Androgenic side effects, such as acne, may be a problem for some women.[5]

Components of progestogen-only pills

Progestogen (micrograms)	**Brand names**
Desogestrel 75	Cerazette
Levonorgestrel 30	Microlut
Norethisterone 350	Noriday 28 Day*

*Fully funded

Risk of venous thromboembolism (VTE)[3, 4]

Circumstance	Risk of VTE per 100,000 women	Relative risk
Healthy non-pregnant women (not taking any oral contraceptive)	About five cases per year	Baseline
COC containing norethisterone (1st generation) or levonorgestrel (2nd generation)	About 15 cases per year of use	three-fold increase
COC containing gestodene or desogestrel (3rd generation)	About 25 cases per year of use	five-fold increase
Pregnancy	About 60 cases per year	12-fold increase

COCs may increase the risk of MI or stroke in the presence of multiple cardiovascular risk factors

There is weak evidence that COCs increase the risk of myocardial infarction and ischaemic stroke, however the absolute risk is still low.[3]

In women with multiple cardiovascular risk factors (e.g. older age, smoking, diabetes, hypertension, obesity or a family history of cardiovascular disease before age 50) the risk may be increased further.

COCs are best avoided in these women, however progestogen only or non hormonal methods can be used.[8]

Important drug interactions

Ethinyloestradiol and progestogens are metabolised by liver enzymes. Induction of these enzymes by certain drugs may affect the plasma concentration of contraceptive hormones. Some anti-epileptics and antibiotics are examples of drugs that may reduce the concentration of hormonal contraceptives and decrease their efficacy. Table 1 provides a list of drugs that interact with oral contraceptives. The list is not comprehensive.

Practice points for oral contraceptive interactions

Liver enzyme inducing drugs:

COCs and POPs are both affected; alternative methods of contraception may be a better choice for women using enzyme inducers long-term.

For short-term use of enzyme inducers, women taking COCs should use a 50 microgram daily dose of ethinyloestradiol and use additional precautions for the duration of treatment and for four weeks afterwards.

Antibiotics:

The antibiotics listed in the table as liver enzyme inducers should be dealt with as above. Although other antibiotics are not liver enzyme inducers, they may temporarily decrease colonic bacteria and therefore inhibit the enterohepatic circulation of ethinyloestradiol.[7] Progestogen is not affected.

Generally the evidence for this interaction is weak and often based on anecdotal reports, however because the consequences of an unwanted pregnancy can be serious the following advice is provided for all antibiotics:

Table 1: Interactions with oral contraceptives[6, 7]

Drug class	Examples	Effect	Examples that do not affect OCs
Anti-epileptics	Carbamazepine Oxcarbazepine Phenytoin Phenobarbital Primidone Topiramate	Induce liver enzymes resulting in a reduction in ethinyloestradiol and progestogen concentrations	Ethosuximide Gabapentin Lamotrigine Levetiracetam Valproate Vigabatrin
Antibiotics	Rifampicin Rifabutin	Induce liver enzymes resulting in a reduction in ethinyloestradiol and progestogen concentrations, breakthrough bleeding	No alternatives
	All other antibiotics narrow- and broad-spectrum	Potential reduction in ethinyloestradiol concentration due to effect on gut flora	

Table 2: Components of combined oral contraceptives (COC)[3, 5, 11]

Oestrogen level **Ethinyloestradiol (micrograms)**	**Progestogen** **(micrograms)**	**Brand names**
20 micrograms	Levonorgestrel 100	Loette Microgynon 20 ED
	Desogestrel 150	Mercilon 21 Mercilon 28
30 micrograms	Gestodene 75	Femodene 28 Minulet 28
	Levonorgestrel 150	Levlen ED* Microgynon 30 Microgynon 30 ED Monofeme* Nordette
	Desogestrel 150	Marvelon 21 Marvelon 28
	Drospirenone 3000	Yasmin
35 micrograms	Cyproterone 2000	Estelle 35 ED* Diane-35 ED
	Norethisterone 500	Norimin*
	Norethisterone 1000	Brevinor 1/21* Brevinor 1/28*
50 micrograms	Levonorgestrel 125	Microgynon 50 ED*
Phasic 30/40/30	Levonorgestrel 50/75 /125	Trifeme 28* Triphasil 28 Triquilar ED
Mestranol† 50 micrograms	Norethisterone 1000	Norinyl 1/28

* Fully funded

† Mestranol is converted in the liver to ethinyloestradiol; 50 micrograms of mestranol is pharmacologically equivalent to 35 micrograms of ethinyloestradiol.[8]

Women on short courses (less than three weeks) of antibiotics should be advised to use additional precautions during the course and until seven consecutive active pills have been taken after antibiotics have been discontinued. This may require missing the inactive pills or the pill-free week.

It is thought that gut flora develop resistance to non-enzyme inducing antibacterials after three weeks of treatment and for this reason additional precautions are not required after this time.[6]

Minor adverse effects

Most COCs contain the same oestrogen (ethinyloestradiol) and for that reason the properties of individual products are based on the amount of ethinyloestradiol in the tablet along with the varying properties of the progestogen (Table 2).

The activity of various progestogens is largely based on animal experiments and how this applies to humans is largely unknown. The dose is often adjusted to make different progestogens approximately equivalent in terms of their activity and for these reasons there is some debate about whether different progestogens are better or worse in terms of side effects or clinical responses.[9]

There is limited clinical evidence to guide pill changes when women experience adverse effects on a particular pill; however there are some principles that may guide choice (Table 3). Often a change in COC type can help to improve some adverse effects as long as it does not increase the risk of more serious medical conditions. Many side effects are commonly experienced in the first three months and may subside after this time therefore it is best to try a particular pill for at least three cycles before switching.[5, 9]

Level of oestrogen affects side effect profile

COCs contain 20–50 micrograms of ethinyloestradiol; 20 micrograms being considered low-strength, 30–40 micrograms standard-strength and 50 micrograms high-strength.

Generally, advice at present is to start with a standard dose pill and a first or second generation progestogen (lower VTE risk) e.g. Levlen, Monofeme or Norimin. These pills are fully funded and cost $3 for six months supply.

GPs may favour using the lowest effective dose of ethinyloestradiol as it would theoretically carry a lower risk of adverse effects associated with oral contraceptive use such as thrombosis or myocardial infarction.

Authors of a Cochrane review compared lower- versus higher-dose oestrogen for contraception. While they could not detect differences in rare adverse effects or contraceptive effectiveness they found lower-dose oestrogen COCs resulted in higher rates of bleeding pattern disruptions and early trial discontinuation.[10]

High-strength preparations containing 50 micrograms of ethinyloestradiol are generally used only in situations

Note on Yasmin

Yasmin contains ethinyloestradiol and the relatively new progestogen, drospirenone. Drospirenone is an analogue of spironolactone therefore caution is required in women with renal impairment or those taking potassium-sparing drugs because there is potential for hyperkalaemia.[3] There is also limited data on VTE risk, however some evidence suggests that the risk of VTE is comparable to that of other COCs (e.g. levonorgestrel)

Yasmin is claimed to have beneficial effects on acne, treating premenstrual syndrome, and less weight change however there is limited evidence of clinically significant advantages over other standard strength COCs.[4, 9] In New Zealand, Yasmin is not funded and would cost a patient approximately $20/month.

Table 3: Combined oral contraceptive adverse effects and potential solutions[3, 5, 10]

Adverse effect	Action needed	Pill Suggestions
Acne	Increase oestrogen Reduce progestogen or change to less androgenic progestogen	Marvelon Femodene Yasmin Estelle 35 ED* Mercilon
Amenorrhoea	Increase oestrogen Decrease progestogen	Norimin* Brevinor-1*
Breakthrough bleeding • Early to mid cycle	Increase oestrogen	Levlen*, Monofeme*, Microgynon 30 Marvelon
• Late cycle	Increase progestogen or change type	Femodene Trifeme*, Triphasil, Triquilar
Breast soreness	Decrease oestrogen Decrease progestogen	Loette, Microgynon 20 Mercilon
Depression, moodiness or irritability	Decrease progestogen	Norimin* Loette, Microgynon 20 Trifeme*, Triphasil, Triquilar
Headache in pill-free week	Tri-cycle pills (skip two pill-free weeks in every three months)	
Menstrual cramps	Increase progestogen or tri-cycle pills	
Nausea	Decrease oestrogen	Loette, Microgynon 20 Mercilon
Weight gain	Decrease oestrogen Decrease progestogen	Loette, Microgynon 20 Mercilon

* Fully funded

where the bioavailability of ethinyloestradiol will be reduced, for example in women who are concomitantly taking enzyme-inducing drugs.[2]

Type of progestogen may affect side effect profile

A Cochrane review that compared various progestogens in COCs found that second and third generation progestogens were preferred to norethisterone (first generation) across all acceptability indices they measured including; effectiveness (pregnancy rates), discontinuation rates, reasons for discontinuation, cycle control, and side effects. It also found that gestodene has comparable contraceptive effectiveness to levonorgestrel and desogestrel and that drospirenone is similar to desogestrel.[12]

The newer progestogens, gestodene and desogestrel are associated with a slightly increased absolute risk of VTE compared with levonorgestrel or norethisterone. Cyproterone acetate has a higher risk and is not generally recommended unless the woman has androgenic features such as acne and hirsutism or polycystic ovary syndrome (see page 12).

Switching COCs

When switching COCs containing different progestogens, the new COC should be started the day after the last active pill has been taken from the previous COC. For 28 day packs, this will mean missing out the seven inactive pills. If a seven-day break is taken before starting the new brand then additional precautions will be required until seven active pills have been taken.

Summary

COCs are generally safe, however their use may need review in some situations.

Medical conditions may arise where a COC is no longer suitable and is best discontinued or the experience of adverse effects may require a trial of a different COC. Drug interactions may affect COC efficacy and additional precautions may be required.

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UK Medical Eligibility Criteria (UKMEC) for combined oral contraceptive use[2]

UKMEC Category 1 – Unrestricted Use

Age – menarche to <40 years

Parity – nulliparous and parous

Breastfeeding – >6 months postpartum

Postpartum – >21 days if not breastfeeding

Post-abortion – immediately first and second trimester, and post-septic

Past ectopic pregnancy

History of pelvic surgery

Minor surgery without immobilisation

Varicose veins

Non-migrainous headaches – mild or severe

Epilepsy – and not using liver enzyme-inducers

Depressive disorders

Vaginal bleeding – unsuspicious irregular, heavy or prolonged

Endometriosis

Benign ovarian tumour

Severe dysmenorrhoea

Gestational trophoblastic neoplasia – when hCG is normal

Cervical ectropion

Breast disease – benign breast disease or a family history of breast cancer

Endometrial or ovarian cancer

Uterine fibroids – with or without distortion of the uterine cavity

PID – current; or past history of, with or without subsequent pregnancy

STI – current, vaginitis or increased risk of STI

HIV/AIDS – risk of HIV/AIDS, current HIV not using antiretroviral therapy

Schistosomiasis, pelvic and non-pelvic tuberculosis, malaria

Diabetes – history of gestational disease

Thyroid disorders

Viral hepatitis – carrier

Anaemias – thalassaemia, iron deficiency

Raynaud's disease – primary without lupus anticoagulant

UKMEC Category 2 – Benefits generally outweigh risks

Age – ≥40 years[a]

Breastfeeding – between 6 weeks and 6 months postpartum and partially breastfeeding (medium to low)

Smoking – aged <35 years, or aged ≥35 years and stopped smoking ≥1 year ago

Obesity – BMI ≥30–34 kg/m2

History of high blood pressure during pregnancy

Family history of VTE in a first-degree relative aged ≥45 years

Major surgery without prolonged immobilisation

Superficial thrombophlebitis

Known hyperlipidaemias – e.g. common hypercholesterolaemia or familial combined hyperlipidaemia

Valvular and congenital heart disease – uncomplicated

Migraine headaches – without aura in women aged <35 years

Vaginal bleeding – suspicious for serious condition before evaluation

CIN and cervical cancer

HIV/AIDS – current HIV using antiretroviral therapy, or current AIDS and using HAART

Diabetes – NIDDM and IDDM, non-vascular disease

Gallbladder disease – asymptomatic or treated with a cholecystectomy

History of cholestasis – pregnancy-related

Inflammatory bowel disease

Sickle cell disease

Raynaud's disease – secondary without lupus anticoagulant

Non-liver enzyme-inducing antibiotics

Highly active antiretroviral therapy (HAART)

UKMEC Category 3 – Risks generally outweigh benefits[b]

Breastfeeding – between 6 weeks and 6 months postpartum and fully or almost fully breastfeeding

Postpartum – <21 days postpartum

Smoking – aged ≥35 years and smoking <15 cigarettes per day, or stopped smoking <1 year ago

Obesity – BMI 35–39 kg/m2

Cardiovascular disease – multiple risk factors for arterial cardiovascular disease

Hypertension – elevated blood pressure >140 to 159 mmHg systolic or >90 to 94mmHg diastolic

Family history of VTE in a first-degree relative aged <45 years

Immobility (unrelated to surgery) – e.g. wheelchair use, debilitating illness

Known hyperlipidaemias – e.g. familial hypercholesterolaemia

Migraine headaches – without aura in women aged ≥35 years; or a past history of migraine with aura at any age

Breast disease – past history of breast cancer and no evidence of recurrence for 5 years; carriers of known gene mutations associated with breast cancer (e.g. BRCA1); undiagnosed mass

Diabetes – with nephropathy/retinopathy/neuropathy; or other vascular disease or diabetes of >20 years' duration (category given will depend on disease severity)

Gallbladder disease – symptomatic medically treated or current

History of cholestasis – past COC-related

Cirrhosis – mild compensated disease

Drugs which induce liver enzymes – e.g. rifampicin, rifabutin, St John's Wort, griseofulvin and certain anticonvulsants (i.e. phenytoin, carbamazepine, barbiturates, primidone, topiramate, oxcarbazepine)

UKMEC Category 4 – Unacceptable health risk and should not be used

Breastfeeding – <6 weeks postpartum

Smoking – aged ≥35 years and smoking ≥15 cigarettes per day

Obesity – BMI ≥40 kg/m2

Cardiovascular disease – multiple risk factors for arterial cardiovascular disease

Hypertension – blood pressure ≥160 mmHg systolic and/ or ≥95 mmHg diastolic; or vascular disease

VTE – current (on anticoagulants) or past history

Major surgery with prolonged immobilisation

Known thrombogenic mutations

Current and history of ischaemic heart disease

Stroke

Valvular and congenital heart disease – complicated by pulmonary hypertension, atrial fibrillation, history of subacute bacterial endocarditis

Migraine headaches – with aura at any age

Gestational trophoblastic neoplasia – when hCG is abnormal

Breast disease – current breast cancer

Diabetes – with nephropathy, retinopathy, neuropathy or other vascular disease, or diabetes of >20 years' duration (category given will depend on disease severity)

Viral hepatitis – active disease

Cirrhosis – severe decompensated disease

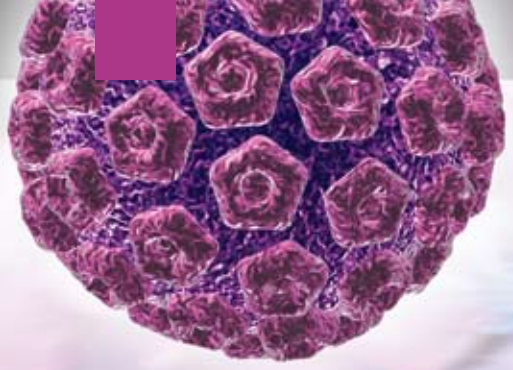
Liver tumours – benign and malignant

Raynaud's disease – secondary with lupus anticoagulant and thus a tendency to thrombosis

a Age ≥40 years: women may use COC until age 50 years if there are no medical contraindications.

b Definition of UKMEC 3 – the risks generally outweigh the benefits but the method can be considered for use with clinical judgement and/ or specialist referral if other methods are unacceptable.

AIDS, acquired immune deficiency syndrome; **BMI**, body mass index; **CIN**, cervical intraepithelial neoplasia; **HAART**, highly active antiretroviral therapy; **hCG**, human chorionic gonadotrophin; **HIV**, human immunodeficiency virus; **IDDM**, insulin-dependent diabetes; **NIDDM**, non-insulin-dependent diabetes; **PID**, pelvic inflammatory disease; **STI**, sexually transmitted infection; **TB**, tuberculosis; **VTE**, venous thromboembolism.



HPV Vaccines: An overview

Contributed by Dr Nikki Turner, Director, Immunisation Advisory Centre, University of Auckland

Human papillomavirus and cervical cancer

Papillomaviruses are a large family of DNA viruses that cause epithelial proliferations or warts. The recognition of the pivotal role of human papillomaviruses (HPV) in the aetiology of cervical cancer led to the development of prophylactic vaccines.[1]

There are over 100 types of HPV and around 30–40 of these are known to infect the genital tract – of these around 15 are known to be oncogenic. In New Zealand, despite an active screening programme, there are still about 200 new diagnoses of cervical cancers per year, and approximately 70 deaths. Māori and Pacific women have disproportionately higher rates of cervical cancer than other women.

HPV is also a significant contributor to other genital tract cancers and is estimated to contribute in up to 85% of anal cancers, 50% of vaginal, vulval and penile cancers, 20% of oropharyngeal cancers and 10% of pharyngo-laryngeal cancers.

Vaccines against HPV

There are currently two vaccines available, both with similar technology targeting HPV 16 and 18 viruses. The key differences are summarised in Table 1.

While the prevalence of HPV types are unknown in the New Zealand population, types 16 and 18 combined are implicated in approximately 70% of cervical cancer internationally and a further six serotypes contribute another 20%.

Gardasil™ is a quadravalent vaccine (four antigens), also containing HPV types 6 and 11 which are not implicated in cervical cancer, but are responsible for over 90% of genital warts, and contribute to low grade cervical abnormalities.

Cervarix™ is a bivalent vaccine (two antigens) with a novel adjuvant, which may enhance the immune reponse.

Clinical trials show that both vaccines are effective and have excellent safety profiles. It is not yet clear whether the differences in formulation will result in any clinical differences in the long term.

Efficacy of vaccines

Combined clinical trial data (involving over 40,000 participants) has shown almost 100% efficacy against persistent HPV infection 16/18 in phase two studies of subjects with no previous exposure. Antibodies levels were 10–80 times higher than those observed in natural infection.[2-5] (N.B. The minimum serum antibody titre to protect from persistent HPV infection remains to be defined).

Efficacy is much lower when looking at outcomes among all subjects, regardless of previous exposure to HPV. In the Future 1 trial there was an efficacy of 20% for reduction

of grade 1–3 CIN or adenocarcinoma in situ (AIS), and this reduction was largely attributable to reduction in lower grade lesions.[6]

Promising early data on cross protection suggests there may be a 38% reduction in CIN2/3 or AIS caused by non-vaccine serotypes which contribute over 20% of cervical cancers.[7]

Duration of immunity

HPV prevalence and incidence peaks at approximately 20 years of age. This leads to peak incidence of CIN in the 25–30 year old age group, and cervical cancer from mid-life.[8] Therefore the duration of induced HPV immunity needs to be at least ten years after adolescent vaccination to protect against persistent HPV infection and subsequent development of CIN2/3.

Current evidence from clinical trials suggests sustained immunity up to five years with no evidence of waning.[9] Continued monitoring of longevity of immunity is underway.

Table 1: Comparison of commercial vaccines (randomised phase 2 studies) Adapted from Adams et al (2007)[1]

	Cervarix (GSK)	**Gardasil (Merck)**
HPV Types	16/18 high risk	16/18 high risk; 6/11 genital wart types
Expression system	Baculovirus	Yeast
Vaccination Schedule	0, 2 ,6 months	0, 1 ,6 months
Antigen dose	VLP 16, 18 (20, 20µg)	VLP 16,18,6,11(40, 20, 20, 40µg)
Adjuvant	ASO_4 [500µg $Al(OH)_3$+50µg MPL]	Alum 225µg[$Al(PO_4)$]
Trial size	560 vacinees; 553 placebo	227 vaccinees; 275 placebo
Trial countries	United States of America, Canada, Brazil	
Age, trial subjects	15–25 years	16–23 years
Duration of follow up	Up to 54 months	Up to 36 months
Efficacy (% CI intervals) (a) HPV infection Incident infection Persistent infection intention to treat (b) Cytological abnormalities (c) HPV 16/18 pre-malignancy	 96.9% (81.3–99.9) 94% (63–99) 97% (84–100) 100% (42–100)	 Not available 89% (73–96) Not published 100% (32–100)
Serious adverse events reported	Nil	Nil
Immune response (a) Seroconverson (b) Antibody titres	 100% 50–80 times natural infection	 100% 10–20 times natural infection

Safety of vaccines

These vaccines are both generally well tolerated with the most common adverse event being local discomfort at the injection site. There have been no discontinuations in trials due to adverse events, and serious adverse events were at similar rates to the placebo groups.

The clinical trial program for Gardasil vaccine safety involved subjects from 33 countries and safety data collected on more than 10,000 subjects aged 9 to 26 years, demonstrated that the vaccine was well tolerated. The most commonly reported adverse event in clinical studies was a mild local reaction at the injection site. Systemic reactions were also usually mild.

Published data on Cervarix also appears to show a good safety profile (data up to 4.5 years).[10]

Common issues with HPV vaccines

All sexually active women are at risk

HPV is very common, and while highly sexually active women are at higher risk of contracting HPV earlier, all sexually active women are at risk. A study found that the risk of HPV infection was 28.5% one year after first sexual intercourse, increasing to almost 50% by three years.[11]

Advice about practising safe sex should still be provided; it is important that women realise that the vaccine does not protect against all types of HPV or other sexually transmitted diseases.

There have been parental concerns expressed around adolescent HPV vaccine promoting promiscuity or earlier sexual activity. To date there is no evidence for this.

Vaccination most effective prior to sexual debut

There is currently no evidence that these vaccines have any therapeutic activity against persistent HPV infection. Consequently, for prophylactic vaccination to be most effective, it should occur prior to sexual debut.[8]

Age of vaccination

Early adolescent girls have been shown to have a better serological response to the HPV vaccine compared with older women. This could theoretically lead to longer lasting immunity.[9] However there is no definite evidence of this.

For women over 25 years the benefit of HPV vaccine is not clear, however there is likely to be benefit for a small group of women who may not have been exposed to infection. The potential benefit of vaccinating women who have successfully eradicated HPV infection with their own natural immunity to prevent re-infection occurring in late life is unknown.

Vaccination advice for the older teenager/young adult

It is difficult to predict the effectiveness of vaccinating for any sexually active individual as it is unclear if they have already acquired the specific HPV serotypes. However it can be expected that many older teenagers/young adults (and possibly older adults as well) would gain from being vaccinated. As the vaccination appears to have a good safety profile there is likely to be more to gain than to lose by offering vaccination to currently sexually active individuals, even when it is unclear of their HPV status.

Vaccination of males

The added value of vaccinating males to attempt herd immunity is currently not clear. Mathematical modelling to date suggested there is little added advantage if HPV vaccination coverage in the female population exceeds 70%.[12]

Potential effect of HPV vaccine on Cervical Screening

HPV vaccination in adolescence with continued cervical screening is projected to ultimately lead to a 76% lifetime reduction in cervical cancer deaths and 50% reduction in cervical screening abnormalities if high vaccination coverage is achieved.[1] In New Zealand there are approximately 30,000 abnormal smear results annually.

If early adolescent girls are vaccinated it will take at least 15 years before a major significant impact on the incidence of CIN2/3 will be seen, and at least 30 years before an impact on cervical cancer is seen.

Cervical screening will need to continue in the presence of a vaccination programme, firstly because there will be a large cohort of women who have been exposed to HPV prior to the onset of a vaccination programme who need surveillance, and because the vaccine does not protect against all types of oncogenic HPV.

Summary

HPV vaccination can be expected to reduce cervical cancer and possibly a range of other orogenital cancers. Vaccines appear to have good safety profiles to date, and duration of immunity is at least five years with ongoing monitoring.

Effectiveness is highest if given to females prior to exposure to HPV; hence the best age to deliver this vaccine is expected to be in the early adolescent period. An HPV vaccine is expected to be introduced soon into the New Zealand vaccination schedule for 11 year old girls. Currently neither vaccine is funded and costs approximately $400–$500.

There are significant implications for community awareness and education around the role of HPV in cervical cancer, the fact that it is a sexually-transmitted disease, and sustaining an ongoing high-quality cervical screening programme.

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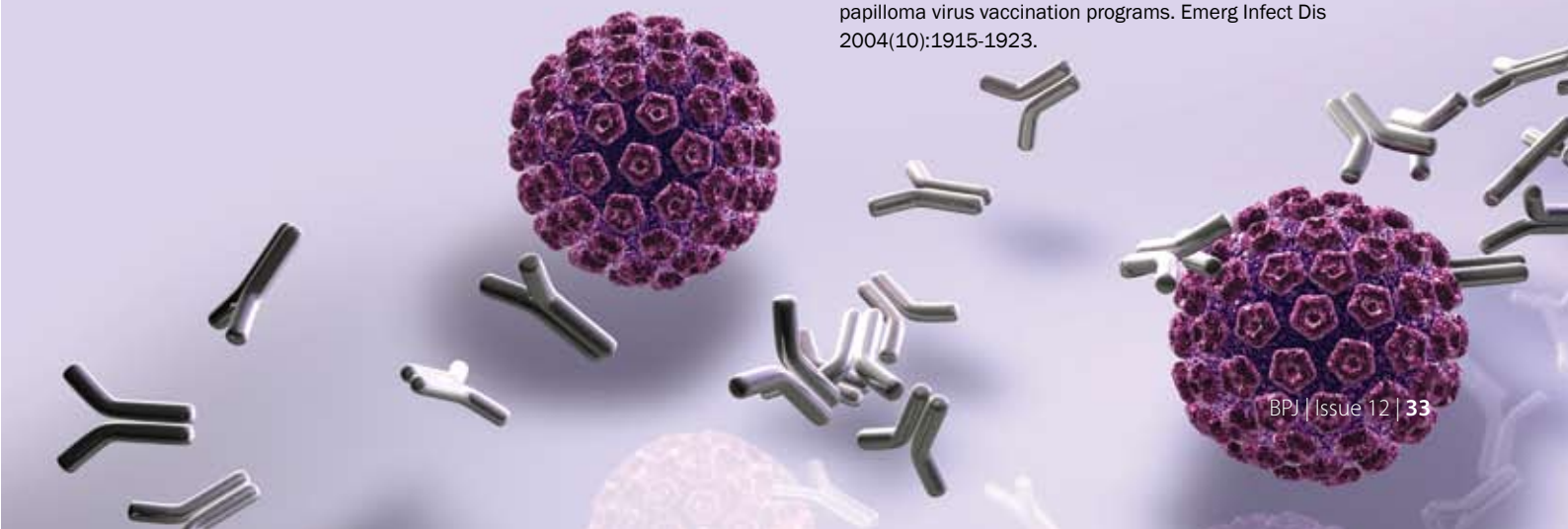
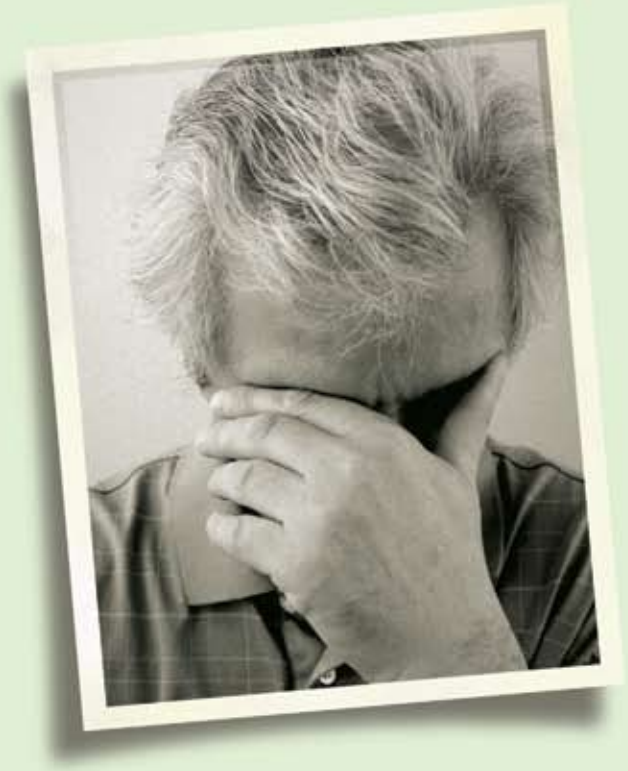


Erectile Dysfunction

Key Advisor: Associate Professor John V Conaglen, Waikato Clinical School, Faculty of Medical and Health Science, University of Auckland

Erectile dysfunction (ED) is defined as the inability to achieve or maintain an erection sufficient for satisfactory sexual activity. Persistent ED is common, particularly in older men, and can significantly impair quality of life both for the man and his partner.



Erectile dysfunction: organic or psychogenic

ED has organic and psychogenic causes. It is increasingly recognised that even for men with an obvious organic cause there are psychological factors that may play a role in either exacerbating or maintaining the difficulty. Men suffering from ED differ in the way they present, the severity of the disorder, and associated co-morbidities.[1] (Table 1)

Distinguishing whether the cause of ED is predominantly organic or psychological may be useful in directing management.

Men with an organic cause for their ED usually present with a gradual onset and the difficulty becomes progressively worse with time. Early morning erections are usually decreased or absent.[2]

When the cause is psychological, the ED may present suddenly with a complete and immediate loss of sexual function which may vary with the partner or situation, or may be indistinguishable from ED caused by organic disease. A useful clinical indicator is that men with psychogenic ED usually have maintained their early morning erections.[1, 2]

Organic and psychogenic causes are not mutually exclusive; many men have components of the two.

Initial diagnosis and management of erectile dysfunction[3]

A detailed history is essential:

- To understand the nature of the patient's complaint, the impact on himself, his partner and their relationship. It is also important to understand how the man and his partner have adapted to the condition which is often present for many years before a man presents to his GP.
- To try and determine the likely cause of ED, i.e. the impact of organic or psychological factors involved.
- To identify co-morbidities (e.g. vascular factors, diabetes mellitus, depression or anxiety) or drugs that may be contributing to ED.
- To ask about other sexual difficulties that may be associated with the ED, i.e. low sexual desire, rapid ejaculation and associated sexual difficulties for the partner (e.g. low desire, vaginal dryness and discomfort).

Table 1: Common causes of erectile dysfunction[2]

Organic	Psychogenic

▪ Vascular disease
▪ Diabetes mellitus
▪ Medications:
  ▫ Antidepressants
  ▫ Psychotropics
  ▫ Antihypertensives
▪ Cigarette smoking
▪ Alcohol
▪ Neurological disorders
▪ Hypogonadism
	▪ Performance anxiety
	▪ Generalised anxiety
	▪ Major depression

Physiology of erection

Sexual stimulation, both physical and mental, directs the release of nitric oxide from the penile nerves. This nitric oxide stimulates the production of cyclic guanosine monophosphate (cGMP) within the vascular smooth muscle of the corpora cavernosae necessary for an erection. In addition, nitric oxide is also released from endothelial cells of the corpora cavernosae to maintain the cGMP levels within the corpora cavernosae smooth muscle. cGMP induces corpora cavernosae smooth muscle relaxation and the vascular lakes of the penis fill with blood. As the penis engorges, the penile veins are passively compressed by increased intracavernosal pressure and this restricts venous return from the penis. A full erection results from the combination of increased blood flow to the penis and decreased venous return. cGMP is degraded to 5'GMP by the action of type 5 cGMP phosphodiesterase (PDE5), returning the penis to the flaccid state.[4] Drugs such as sildenafil, tadalafil and vardenafil (PDE5 inhibitors) act by inhibiting this enzyme.

Physical examination should be tailored to the individual clinical presentation:

- Given the association of ED with cardiovascular disease, cardiovascular risk assessment may be appropriate.
- Genital examination can occasionally identify anatomical abnormalities and signs of hypogonadism, but more importantly may reassure the patient that the doctor is taking the condition seriously.
- As diabetes is a risk factor for ED and undiagnosed diabetes may be present in men with ED, assessment for complications of diabetes may be useful.
- Digital rectal examination can be used to identify suspected prostate disease.

Physical examination may guide further investigations:

- If unexplained low libido or suspected hypogonadism, measure testosterone and prolactin at 0800hrs.
- Laboratory tests useful as part of a cardiovascular risk assessment may include blood glucose and fasting lipids.
- Other investigations, such as thyroid function tests, renal and liver function tests, and a complete blood count, may be done on a case by case basis.

Treat the cause of erectile dysfunction wherever possible:

- It is desirable to obtain the views of the partner as to both the cause and what she or he would like to do about the difficulty.
- Consider psychological intervention for psychogenic erectile dysfunction.
- Although predominantly organic ED rarely benefits from modification of risk factors (Table 2) or a change from any possible drug causes (Table 3), the general health of the patient may be improved by attention to these issues.

Specific treatment options for erectile dysfunction

Treatments for erectile dysfunction include oral therapy with phosphodiesterase type 5 inhibitors (PDE5 inhibitors), injection therapy, and penile devices. Testosterone therapy should only be used in men with established hypogonadism. Psychotherapy should be considered in all men who have a psychogenic component to their erectile dysfunction.[5]

Table 2: Risk factors for erectile dysfunction[5]

Risk Factor	Treatment
Metabolic syndrome	Diet, exercise and weight loss
Cardiovascular disease	May use PDE5 inhibitor with caution. For some patients, specialist review is recommended (Box 1). Use of PDE5 inhibitors is contraindicated with concomitant nitrates.
Tobacco smoking	Smoking cessation
Social or relationship stress, depression	Counselling, lifestyle change, medical treatment
Endocrine disorders such as hypogonadism, hypo- or hyperthyroidism	Correction of underlying endocrine disorder; and if needed, possible use of a PDE5 inhibitor
Diabetes	Appropriate glycaemic management

Box 1: ED and coronary heart disease

PDE5 inhibitors are contraindicated until cardiac status is stabilised in the following conditions:[5, 6]

- Unstable angina
- Uncontrolled hypertension
- Congestive heart failure (NYHA III, IV)
- Very recent myocardial infarction (less than two weeks ago)
- High risk arrhythmias
- Obstructive hypertrophic cardiomyopathies
- Moderate to severe valve disease

Best practice tip

A Nelson GP offers a best practice tip for questions that can be asked to establish a patient's suitability for PDE5 treatment:

- Does exertion, stress or sexual activity cause any symptoms?
- What is the most strenuous physical activity that you currently do?
- Do you accept the risk of taking this medication?

Table 3: Drugs associated with erectile dysfunction[4, 5]

Drug class	Examples	Possible alternative with lower risk of erectile dysfunction
Antihypertensives	Beta blockers, calcium channel blockers	ACE inhibitors
Diuretics	Thiazides, spironolactone	Loop diuretics
Antidepressants	Selective serotonin reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors	Limited evidence to guide alternative; specialist review required for any change
Antipsychotics	Phenothiazines, carbamazepine, risperidone	Limited evidence to guide alternative; specialist review required for any change
Hormones	Cyproterone acetate, oestrogen, 5α-reductase inhibitors (e.g. finasteride)	Limited evidence to guide alternative; specialist review required for any change
Dyspepsia and ulcer healing drugs	H_2 antagonists	Proton pump inhibitors
Recreational drugs	Alcohol, marijuana, cocaine	Discontinue use

PDE5 inhibitors are recommended first line therapy

The PDE5 inhibitors currently available are; sildenafil (Viagra), tadalafil (Cialis), and vardenafil (Levitra). They improve erectile function by inhibiting type 5 cGMP phosphodiesterase, thereby increasing penile cyclic guanosine monophosphate (cGMP) which mediates relaxation of cavernosal smooth-muscle cells.[7]

The main difference between the PDE5 inhibitors is the longer half-life of tadalafil at approximately 18 hours compared with approximately four hours for sildenafil and vardenafil.[8]

There is insufficient evidence to support the superiority of one agent over the others and patient preference will usually guide selection.

The PDE5 inhibitors are not funded and vary in price from approximately $80 to $115 for a pack of four tablets.

PDE5 inhibitors are contraindicated in patients taking organic nitrates

PDE5 inhibitors potentiate the hypotensive effects of organic nitrates and therefore the concomitant use of nitrates is contraindicated.[8] The safe time interval, if nitrates need to be used in a medical emergency, has not been determined. Most recommendations suggest withholding nitrate therapy for 24 hours after sildenafil and vardenafil, and 48 hours after tadalafil have been taken.[7]

If the patient requires nitrates after taking a PDE5 inhibitor a cardiologist should be consulted immediately.

PDE5 inhibitors require sexual stimulation to have an effect

PDE5 inhibitors do not cause erections in the absence of sexual stimulation. It is essential for the doctor prescribing PDE5 inhibitors to educate men in the need for sexual stimulation to ensure the drug is effective. Some men who initially fail to respond to a PDE5 inhibitor can be successful with these medications after being correctly educated about their use.[7] As anxiety can over-ride the effect of a PDE5 inhibitor, a patient should not be considered to have failed in the use of a particular PDE5 inhibitor until they have tried them on five to six occasions.

PDE5 inhibitors need to be taken at least 30 minutes to one hour before sexual activity and taking sildenafil with fatty food and/or alcohol may delay its onset of action.

Monitor for adverse effects and therapeutic response

Common adverse effects such as headache, flushing, gastric upset, diarrhoea, nasal congestion, and light-headedness are similar for all three PDE5 inhibitors and are often the result of PDE inhibition in other parts of the body.[7]

Sildenafil and vardenafil have some cross-reactivity with PDE6 and produce visual side effects on rare occasions.

Testosterone therapy is not usually indicated for ED in men with normal testosterone levels.[8]

Testosterone replacement is appropriate when a man with ED is established to have hypogonadism.[1] Gynaecomastia, increased haematocrit, alterations in lipid profile, hypertension, and infertility are some side effects associated with exogenous testosterone therapy.

It also is possible that testosterone may increase the risk of prostate cancer and the risk of treatment versus benefit should be considered and discussed with the patient.

N.B. Hyperprolactinaemia of any cause may result in ED and appropriate management of the raised prolactin may restore normal erections.

PDE5 inhibitors tend to be less effective in the presence of reduced neural nitric oxide release as is the case in men with diabetes.[9]

Injection therapies are usually second line treatments

If oral therapy with PDE5 inhibitors fails or if they are contraindicated or not tolerated, injection therapy may be required.

Intracavernosal injections

These agents act by directly relaxing smooth muscle in the corpora cavernosum and result in an erection.[10] Unlike PDE5 inhibitors, they do not require sexual stimulation to work.

Side effects include pain at the injection site and priapism, and long term use can result in scarring of the tunica albuginea with potential curvature and shortening of the penis.[2]

It is generally recommended that the first dose be administered under medical supervision because of the small risk of priapism and the importance of detailed education in the technique of self-injection.[5]

Alprostadil (Caverject) is the most commonly used agent in New Zealand. Other injectable agents include; an aviptadil and phentolamine combination (Invicorp) and papaverine. Caverject and Invicorp are not funded, however the papaverine injection is. Papaverine is associated with a higher incidence of priapism and scarring of the tunica albuginea and should only be used as a second-line therapy by experienced practitioners.

Penile devices may be suitable for men who fail to respond to other therapies

Vacuum constriction devices and penile prosthetic devices are options for men who fail to respond to other therapies.

Vacuum devices draw blood into the penis by means of a vacuum and a constriction band is applied to retain the blood. Adverse effects include pain, numbness, bruising, a cold blue penis and difficulty with ejaculation. These devices require significant education in their use and the constriction band should not be applied for any longer than 30 minutes.

Penile prostheses are usually malleable or inflatable devices which are surgically implanted into the penis. They are expensive and should only be implanted by an experienced surgeon who is regularly performing the procedure. Due to their permanence they must not be considered until all less invasive options have been tried and failed.[2]

Summary

Erectile dysfunction is common, with increasing prevalence as men age.

A detailed history is essential to identify the possible cause and reveal any factors contributing to the ED such as underlying medical conditions or medication use. As sexual dysfunction usually impacts on the relationship with the partner it is best to try and obtain the views of the partner on both the impact of the ED and its management.

PDE5 inhibitors are first-line therapy for most men with ED. Testosterone should be reserved for those men with hypogonadism. Injection therapy may be appropriate in men who fail to respond to PDE5 inhibitors, are intolerant to them or have contraindications to their use.

Penile devices are usually reserved for men who fail to respond to all other therapies.

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Should **antidepressants** be used to treat **depression** in children and adolescents?

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www.bpac.org.nz keyword: childdepression

Summary of advice:

- Antidepressants may increase suicidal thoughts, but there is no compelling evidence of an increased risk of actual suicide.
- Behavioural therapy and other psychosocial interventions are considered first line treatment for depression in young people.
- If drug therapy is indicated, fluoxetine is the best choice of antidepressant for adolescents or children.
- It is important to maintain regular contact with young patients with depression and to monitor the risk of suicide, especially in the few weeks following a first antidepressant prescription.

Depressive disorder is a major health issue for adolescents in New Zealand, affecting between 4 to 8% of 15 year olds, rising rapidly to rates of 17 to 18% by the age of 18.[1-6] In young people, depressive disorder is pervasive and affects not only function but overall development.[7] It is associated with poor academic functioning, social dysfunction, substance abuse, attempted and completed suicide.[7-12] Co-morbidity is high, with up to half of those with major depressive disorder having another psychiatric disorder at some stage in their life.[7-13]

Despite this high prevalence, it is estimated that over three quarters of depressive disorder in adolescents is undetected. Health professionals are being encouraged to screen for depression and to provide treatment. However FDA black box warnings about the potential for newer antidepressants to increase the risk of suicide have led to concern about the place of antidepressants in the management of depressive disorders in children and adolescents.

Monitoring suicide risk

Monitoring suicide risk is complex. The New Zealand Guidelines Group offers practical advice on how to investigate suicidal ideation. Questions a clinician may consider include:

- How has your mood been lately?
- Has anything been troubling or worrying you?
- Have you had times when you have been feeling sad or down?
- Have you ever felt like life is just getting on top of you?
- Do you sometimes wish you could just make it all stop, or that you could just end it?
- Have you thought about how you might do this?
- Have you ever wished you were dead?
- Have you ever thought about taking your own life?

If the patient endorses any of these statements, the clinician then needs to determine level of intent, existence of a plan, access to means, underlying mental health problems and availability of support and protective factors.

From guideline "Assesment and Management of People at Risk of Suicide". Complete document available from:

http://www.nzgg.org.nz/guidelines/0005/Appendix_2_Assessment_Risk.pdf

How should depression in young people be treated?

There are two major approaches to managing depression in children and adolescents – psychological and pharmacological.

Choosing a treatment involves a team approach including GP, family and patient. With more severe depression, specialist mental health professionals should also be involved. There is no simple tool for determining who will and who will not respond to treatment.

More detailed information on how to assess risk and manage depression can be found in the UK based National Institute of Clinical Excellence (NICE) guidelines and the Guidelines for Adolescent Depression in Primary Care (GLAD-PC) toolkit. This document contains useful flow charts for clinical management and assessment. The New Zealand Guidelines Group (NZGG) is due to release their guidelines on treating depression in children and adolescents shortly.

Websites and a list of resources can be found at the end of this article.

Psychological treatments recommended as first line

There is evidence that cognitive behavioural therapy and interpersonal therapy are both effective in the treatment of depression in children and adolescents.[14, 15] Psychological therapies are recommended as first line treatment, especially in mild to moderate depression.[10, 16] Even for more severe depression up to 13% of young people respond to support and monitoring.[17]

A "stepped care" method should be used, so that simpler and less risky approaches are tried first, dependent on severity of depression. For mild depression, start with "active monitoring" followed by one of the psychological therapies if there is no response.[10, 16] For more severe depression, specialist referral is recommended.

For active monitoring:

- Provide psychoeducation (educate about depression, how to treat it and how to recognise signs of relapse)
- Provide supportive counselling
- Facilitate parental and patient self-management
- Refer for peer support
- Regularly monitor for depressive symptoms and suicidality

 See GLAD-PC toolkit for a clinical management flow chart.

Referral to a child and adolescent mental health service or to a clinical psychologist is currently the best method for accessing psychological treatment, but may not be available in all areas. Other resources could be trialled where psychological therapies are unavailable (see below).

Training for health professionals:

- The Werry Centre in Auckland runs occasional workshops to teach cognitive strategies that can be used as a first step. Contact **coordinator@werrycentre.org.nz**
- The University of Auckland offers two papers teaching cognitive behavioural therapy for children and adolescents (block teaching, suitable for people from anywhere in New Zealand). For information contact **Janine Joubert (j.joubert@auckland.ac.nz)**
- The University of Otago (Christchurch School of Medicine) offers occasional workshops on Interpersonal Therapy training, as well as post graduate courses. For information contact **Associate Professor Sue Luty (sue.luty@otago.ac.nz)**

Fluoxetine in combination with cognitive behavioural therapy

If young people fail to respond to simpler approaches, if their depression is more severe or if psychological treatments are unavailable, fluoxetine may be considered. Combining fluoxetine with cognitive behavioural therapy is an effective treatment option.[18]

- A meta-analysis of the effectiveness of tricyclic antidepressants did not provide convincing evidence of effectiveness of these medications for children and adolescents.[19]
- Authors of a number of meta-analyses of SSRIs and other newer generation antidepressants concluded that the risk benefit ratio is only favourable for fluoxetine.[18–21]
- There is limited evidence that the other medications have anything more than a placebo response. Even for fluoxetine the overall response rate is low.[22]

GPs may wish to consider consulting with a child psychiatrist before prescribing an antidepressant to a person under 18 years. Although there is little evidence to support the use of antidepressants other than fluoxetine, they may be effective for individuals.

The Child and Adolescent Psychiatry Trials Network, based in the USA, has recently commenced work on a "safety registry" for newer antidepressants. It is hoped to identify factors that predict benefit and harm and who should and should not receive a particular medication.[23]

Other resources for treating depression in young people

Because of the limited availability of psychological therapies there has been some interest in the use of technology to deliver these interventions by way of the internet or computer games. Trials show computerised cognitive behavioural therapy compares well with that delivered by

a therapist and is a recommended intervention for adults in the NICE guidelines. Trials for adolescents lag behind but resources are being developed. The Australian based Inspire Foundation has created "Reach Out Central", a user-friendly web-site with an interactive problem solving game for teenagers. This has not been evaluated but could be suggested as a self-help resource alongside active monitoring of mood and suicidal ideation.

In New Zealand, the Ministry of Health have produced a user friendly website aimed at young adults as part of their National Depression Initiative. "The Lowdown" provides interactive resources, chat and support.

Facilitating lifestyle changes, including regular exercise is also an effective management technique.

Useful websites and further reading

You can also visit these websites by linking from this article on the bpac website: http://www.bpac.org.nz

Guidelines

- NICE (UK) guidelines on depression in children and young people:

http://www.nice.org.uk/guidance/index.jsp?action=download&o=29856 (full guideline)

http://www.nice.org.uk/guidance/index.jsp?action=download&o=29858 (brief version)

- Guidelines for adolescent depression in primary care (GLAD-PC): http://pediatrics.aappublications.org/cgi/content/full/120/5/e1313

- GLAD-PC toolkit for primary healthcare professionals:

http://www.glad-pc.org/documents/GLAD-PCToolkit.pdf

- The New Zealand Guidelines Group is due to release a set of guidelines on the management of adolescent and child depression in primary care. The guidelines are drafted and are ready for consultation. http://www.nzgg.org.nz

Resources

- The Lowdown – Ministry of Health initiative, interactive website for young people: http://www.thelowdown.co.nz/

- Reach Out Central – information, support, and an interactive game for youth 16-25 years: http://www.reachoutcentral.com.au/

- Think Good - Feel Good: A Cognitive Behaviour Therapy Workbook for Children and Young People by Paul Stallard: a self-help book available as a paper back and as an e book. ISBN: 978-0-470-84290-4, Paperback, 198 pages, September 2002.

Other websites

- Child and Adolescent Psychiatry Trials Network: https://www.captn.org/

- The Werry Centre: http://www.werrycentre.org.nz

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The investigation of **coeliac disease**: A follow up

Contributed by: Dr Richard Steele, Clinical Immunologist and Immunopathologist, Wellington Hospital and Aotea Pathology.

In BPJ 9 (October 2007), we addressed the topic of managing coeliac disease in primary care. There are a number of tests available for diagnosis and monitoring and there is some confusion over which tests to use and when. We invited Immunologist, Dr Richard Steele who has a special interest in coeliac disease to provide some clarification.

Key Points

- IgA TTG should be the only test for coeliac disease used in general practice.
- Duodenal biopsy is required to confirm diagnosis.
- There are a number of reasons why IgA TTG tests may be negative in a person with coeliac disease so clinical judgement is important.
- Testing for anti-gliadin antibodies (AGA) is unnecessary for either the diagnosis of coeliac disease or 'gluten sensitivity'.

Background

Coeliac disease is a common but often unrecognised disorder, affecting about 1% of the population in New Zealand.[1] It is unknown what the identification rate is in New Zealand, but some countries with comprehensive health systems have identification rates of only about 10%.[2] The appropriate use of laboratory tests for coeliac disease in primary care is crucial to increase this number.

Over the years, there have been a significant number of tests used to screen for coeliac disease. The variety of tests reflects the progression in our understanding of coeliac disease over the past three decades.

IgA TTG should be the only test used in general practice

The IgA anti tissue transglutaminase antibodies (IgA TTG) assay has been shown to have a high sensitivity (90-98%) and specificity (90-99%) for coeliac disease and is therefore the only test required in primary practice.[3-5]

In adult patients with a low probability of coeliac disease, the TTG test has high negative predictive value, therefore a negative test result would virtually exclude the condition. Patients with a positive test result require confirmation by endoscopic duodenal biopsy while still on a gluten containing diet.

On the laboratory request form, indicate "IgA TTG" rather than ambiguous requests such as "coeliac screen".

There are however a number of situations where a negative IgA TTG test does not exclude coeliac disease. In these situations the clinician must have a lower threshold for referral for upper gastrointestinal endoscopy and duodenal biopsy.

Why a negative IgA TTG test may not exclude coeliac disease

Studies show that up to 10% of people with coeliac disease are antibody negative.[3] The reasons for this antibody negative status are unknown. If a person has a negative IgA TTG and is still suspected of having coeliac disease, the clinician should assess the likelihood of coeliac disease based on known risk factors, for example, first degree relatives of patients with coeliac disease, presence of gastrointestinal symptoms, iron deficiency anaemia and type I diabetes.[2]

Antibodies are only present with a normal gluten containing diet, so IgA TTG testing and duodenal biopsy should not be performed in people on a gluten free diet. The length of time needed to be on a gluten containing diet and the amount of gluten required varies with the individual.[6] A practical approach to this would be to recommend a normal diet (at least four slices of bread per day) until the patient becomes symptomatic and for at least one to two months.[4] Studies have shown that 70-90%[7, 8] of patients with a positive IgA TTG test will revert to negative after 12 months on a strict gluten-free diet. The tests can become negative in over 50% of patients after three months.[9]

IgA deficiency has been reported to be increased in people with coeliac disease.[10] If a patient is found to be IgA deficient (total IgA less than 0.05g/L), IgA based testing for coeliac disease such as the IgA TTG is usually negative. The frequency of coeliac disease in people with IgA deficiency varies, however in one study, the prevalence of coeliac disease in 126 children with IgA deficiency was found to be 8.7%.[11] If a person is IgA deficient, some experts suggest IgG based coeliac disease testing, while others suggest going directly to duodenal biopsy, if the clinical suspicion of coeliac disease is high. IgG TTG testing has shown a reasonable sensitivity and specificity in limited case series but further study in this area is needed.[12]

IgA TTG antibody testing is less reliable in children. It takes a somewhat more mature immune system to make some of the "anti-self" antibodies, therefore a child may not have detectable IgA TTG levels until several years after the introduction of gluten into the diet. In addition, in one study, about 50% of children who were initially IgA TTG positive became negative later in childhood despite staying on a gluten containing diet.

People with coeliac disease who are immunosuppressed are thought to be more likely to have negative coeliac disease tests and also normal duodenal biopsies. There is however little evidence of this at present.

Anti-gliadin antibodies and "gluten sensitivity"

Anti-gliadin antibody (AGA) testing is now redundant for the diagnosis of coeliac disease.

AGA testing gained popularity in the 1980s as a test for coeliac disease. It was the first widely available test that could be used for screening. The overall performance of AGA for diagnosing coeliac disease is inferior when compared to IgA TTG.[13-15] There is also significant variation in the performance of the different testing kits available. This test should not be requested in primary care when considering the diagnosis of coeliac disease as it will lead to higher rates of false reassurance or unnecessary duodenal biopsies depending upon the result.

Because of its historical importance and the high rate of false positives, AGA testing has perpetuated and popularised the diagnosis of "gluten sensitivity" (sometimes referred to as "gluten intolerance"). Gluten sensitivity can be termed a syndrome where patients attribute a wide variety of predominantly gastrointestinal, dermatological

and neurological symptoms to the ingestion of gluten containing foods, where the diagnosis of coeliac disease has been reasonably excluded.

Antibodies to gliadin are common, occurring in up to 20% of the population depending upon the assay used and isotypes tested.[16] Studies comparing the frequency of these antibodies in various diseases including psoriasis and multiple sclerosis compared to healthy controls usually show no increase.[17-19]

There are no robust scientific studies to support the testing of AGA in the diagnosis of gluten sensitivity. People who suspect they have gluten sensitivity should be counselled that AGA testing is not reliable in diagnosing this syndrome. For the management of such patients the following steps are suggested:

1. Exclude other diagnoses based on the clinical presentation.
2. Discuss with the patient the pros and cons of the gluten-free diet including the issues of cost and convenience.
3. Referring selected patients to a dietician with clinical expertise in food intolerance can be very helpful. The dietician can assess the nutritional adequacy of the diet and consider food challenges, if appropriate.

In summary, there has been a significant evolution in the serological testing for coeliac disease and further advances are likely to occur in the near future. At present IgA TTG is the recommended test for coeliac disease.

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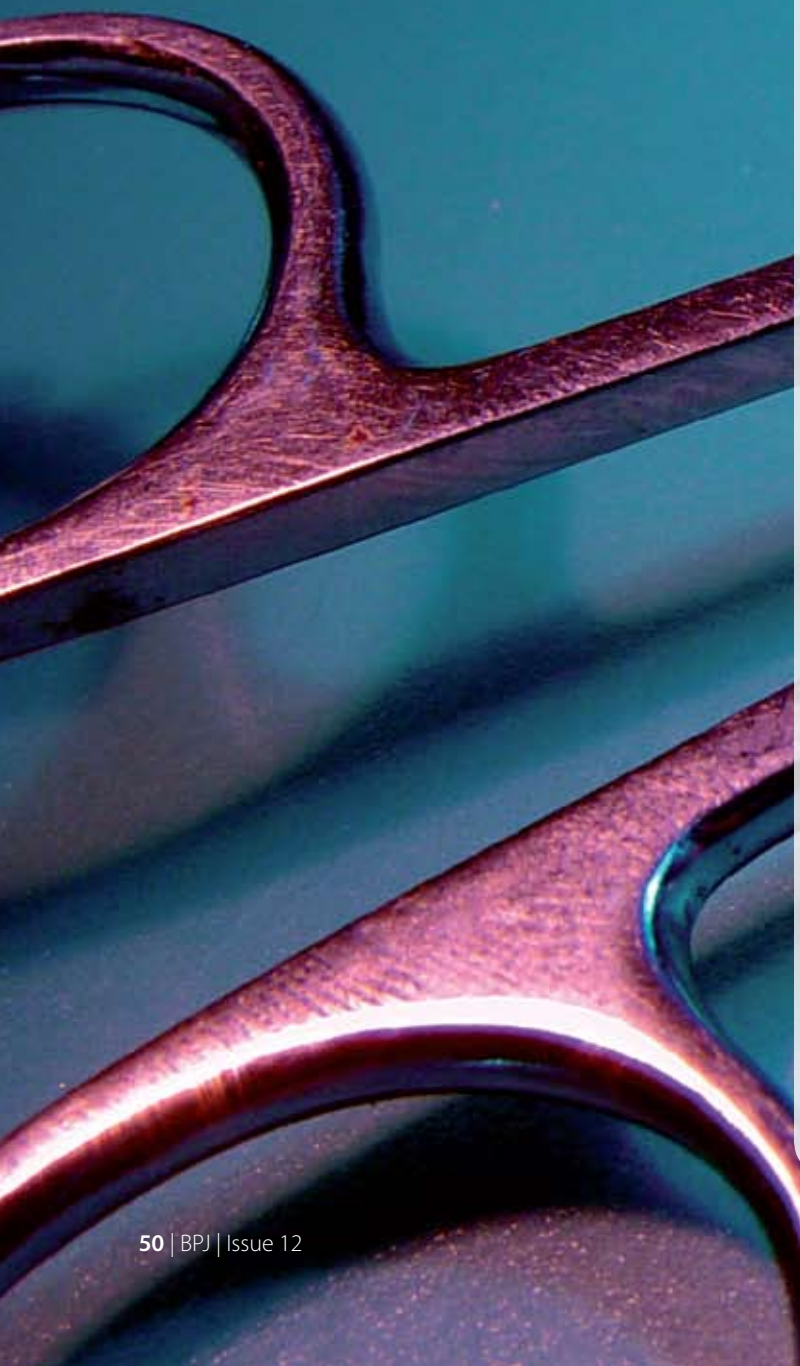

Women using depot medroxyprogesterone (Depo-Provera) for longer than two years do not usually require bone scans

It is generally accepted that the use of Depo-Provera results in reduced bone mineral density (BMD). The reduction in bone mineral density occurs in the first two to three years of use and then stabilises.[1] This is of particular concern in young adolescent women who have not yet attained their peak bone mass, long term users and in older women who may be starting to lose bone mass.

In 2004 the UK Committee on the Safety of Medicines issued a warning regarding bone loss with Depo-Provera use and made the following recommendations:[1]

- In adolescents, Depo-Provera should be used only when other methods of contraception are inappropriate.
- In all women, benefits of Depo-Provera beyond two years should be evaluated against risks.
- In women with risk factors for osteoporosis a method of contraception other than Depo-Provera should be considered.

The FDA also issued a similar “black box” warning in November 2004.[2]

A study showed that many people had interpreted this advice as a warning against using Depo-Provera for longer than two years,[3] however this is not the case. Depo-Provera can be used for longer than two years, as long as the patient is regularly reviewed. There is some evidence that women who switch contraceptive methods tend to switch to a less effective one and possibly by restricting the use of Depo-Provera the number of unintended pregnancies could increase.[3]

Risk factors for osteoporosis include metabolic bone disease, excessive alcohol use, cigarette smoking, anorexia nervosa, a family history of osteoporosis and long-term use of drugs that can reduce BMD (e.g. anticonvulsants, corticosteroids).[4]

Recommendations:

- There is evidence that bone mineral density recovers after discontinuation of Depo-Provera.[5]
- There is a lack of evidence that suggests the decrease in bone density is associated with increased risk of fracture.[5, 6]
- Depo-Provera is useful in women who find it difficult to remember to take a pill every day or who are intolerant of oestrogen.[7]
- After counselling about the use of other contraceptives that do not reduce bone mineral density, the benefits of Depo-Provera in young people generally outweigh the risks.[7]
- More frequent follow-up may be appropriate for young people than adult contraceptive users.[7]
- Follow up of all Depo-Provera users at two years is recommended and should involve clinical history-taking, lifestyle assessment and a discussion of the balance between the benefits and potential risk, however bone scans are not routinely required.[7]

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Evidence That Counts

Acupuncture for Knee Osteoarthritis?

Exercise therapy (strengthening, stretching, functional exercises) has been shown to improve the symptoms of knee osteoarthritis, but the role of acupuncture remains controversial. British investigators performed this randomised trial to lessen the controversy.

Participants were 352 adults (age ≥50) with a clinical diagnosis of knee osteoarthritis. They were assigned to receive advice and exercise, advice and exercise plus true acupuncture, or advice and exercise plus nonpenetrating acupuncture; follow-up was 12 months. The exercise intervention consisted of up to six 30-minute sessions, as did the acupuncture interventions.

At 6 months, the primary outcome — change in pain level — did not differ among the three groups. All three groups improved. At 12 months, the same pattern continued for all three groups. Other outcomes — including global assessment and functional status — did not favour any group. However, small but statistically significant benefits were seen in relief of pain intensity and unpleasantness for up to 12 months in the nonpenetrating acupuncture group, which also reported significantly greater satisfaction with care than the group receiving advice and exercise alone.

Comment:
In this well-designed study, true acupuncture provided no additional benefit over advice and exercise for knee osteoarthritis. Although a few sham acupuncture–controlled trials have suggested that true acupuncture is effective, a recent meta-analysis (which included seven sham-controlled trials) concluded that the average benefit is "clinically irrelevant" and that "placebo or expectation effects" are largely responsible for the perceived benefit of acupuncture in knee osteoarthritis (JW Aug 1 2007, p. 120, and Ann Intern Med 2007; 146:868).

— Keith I. Marton, MD

Foster NE et al. Acupuncture as an adjunct to exercise based physiotherapy for osteoarthritis of the knee: Randomised controlled trial. BMJ 2007 Sep 1; 335:436.

Lactobacillus Helps Prevent Antibiotic-Related Diarrhoea

Probiotics, defined as live microorganisms that offer a health benefit to the host when consumed in adequate amounts, are increasingly recommended for treating or preventing a variety of gastrointestinal ailments. British investigators assessed whether a probiotic preparation would reduce the incidence of antibiotic-related diarrhoea and *Clostridium difficile*–associated diarrhoea among 135 hospitalised patients receiving antibiotics.

The patients (mean age, 74) were randomly assigned to receive either a placebo (sterile) milkshake or a commercial yogurt drink containing three kinds of lactobacilli. The drinks were administered twice daily during the antibiotic course and for a week thereafter. Antibiotic-associated diarrhoea occurred in 12% of the treated patients and 34% of the control patients. *C. difficile* toxin was identified in none of the treated patients and in 17% of control patients. A multivariate analysis that controlled for a number of other confounding factors found that probiotic use reduced the chances of antibiotic-associated diarrhoea by 75%. The estimated cost of preventing one case of diarrhoea was US$100, and the cost of preventing one case of *C. difficile*

diarrhoea was US$120. The makers of the yogurt drink contributed funding to the study.

Comment:

This study strongly supports probiotic use in elderly patients about to receive a course of antibiotics. Its major weakness is the extremely high exclusion rate in recruiting people for this study, so its generalisability remains to be determined.

— Keith I. Marton, MD

Hickson M et al. Use of probiotic Lactobacillus preparation to prevent diarrhoea associated with antibiotics: Randomised double blind placebo controlled trial. BMJ 2007 Jul 14; 335:80.

Proton-Pump Inhibitors for Uncomplicated Dyspepsia?

Patients with dyspepsia are commonly treated empirically with proton-pump inhibitors. However, the data supporting this practice are not clear-cut. In this randomised trial from Hong Kong, researchers enrolled 157 young adults (age range, 18–45) with at least three months of dyspepsia during the preceding year, no alarm symptoms, a negative breath test for *Helicobacter pylori*, and no recent exposure to nonsteroidal anti-inflammatory drugs. Dyspepsia was defined as pain or discomfort centred in the upper abdomen; patients with predominant oesophageal reflux or irritable bowel symptoms were excluded.

Patients received lansoprazole (30 mg daily) or placebo for 12 weeks. At 4, 12, and 26 weeks, mean scores on a standardized dyspepsia scale improved slightly in both groups, with no differences between groups. At 12 weeks, similar proportions of lansoprazole and placebo recipients had complete resolution of symptoms (13% vs. 17%). During a one year of follow-up, healthcare utilisation and endoscopy rates also were similar in the two groups.

Comment:

In this study, young otherwise healthy *H. pylori* negative patients with dyspepsia derived no benefit from proton-pump inhibitor therapy. It is important to note that this population was highly selected: Patients likely to have reflux or peptic ulcer were excluded. For patients like the participants in this trial, the optimal approach to dyspepsia remains unclear.

— Allan S. Brett, MD

Leung WK et al. Initial treatment with lansoprazole in young dyspeptic patients with negative urea breath test result: A randomized controlled trial with 12-month follow-up. Am J Gastroenterol 2007 Jul; 102:1483-8.

What's the Best Treatment for Painful Diabetic Neuropathy?

A variety of drugs are used to treat painful diabetic neuropathy, and most have been evaluated in randomised trials. This systematic review provides a useful comparison of the efficacy of the various treatments.

Among eligible randomised controlled trials that compared one or more drugs with placebo in adults with painful diabetic neuropathy, ten trials (1576 patients) evaluated anticonvulsants, four (94 patients) evaluated antidepressants, three (329 patients) evaluated opioids, two (805 patients) evaluated duloxetine, and one (277

patients) evaluated capsaicin cream. The treatment period in all studies was less than 6 months.

The efficacy of these drugs in reducing pain by 50%, in descending order from most to least effective, was as follows: tricyclic antidepressants, traditional anticonvulsants (i.e., sodium valproate and carbamazepine), opioids, newer generation anticonvulsants (i.e., pregabatin and gabapentin), duloxetine, and capsaicin. Patients given traditional anticonvulsants and tricyclic antidepressants were least likely to withdraw from studies because of adverse effects.

Comment:
All these studies are limited by the short treatment periods. Given that caveat, tricyclic antidepressants and traditional ant vulsants still appear to be the first-line drugs of choice for painful diabetic neuropathy.

— Keith I. Marton, MD

Wong M-C et al. Effects of treatments for symptoms of painful diabetic neuropathy: Systematic review. BMJ 2007 Jul 14; 335:87.

Is mobile phone use associated with increased risk of brain tumours?

Evidence-Based Answer
Although the investigations into this question have been case-control studies, and hence subject to significant bias, the accumulating evidence from multiple populations does not support the idea that mobile phone use places individuals at increased risk of brain tumours. (SOR B, based on several case-control studies.)

In a study of 469 men and women aged 18 to 80 years with primary brain cancer and 422 matched controls without brain cancer, no association was found for history, frequency, or duration of mobile phone use.[1] Another case-control study matched 782 cases (489 gliomas, 197 meningiomas, 96 acoustic neuromas) with 799 controls, and found no association with frequency or duration of mobile phone use, nor with specific subtypes of brain tumours.[2] Subsequent studies have had similar findings.[3,4] A recently published analysis examined whether an association exists between mobile phone use and the development of the most common type of central nervous system cancer, glioma.[5]

In the largest study to date to examine this relationship, researchers interviewed 966 people aged 18 to 69 years diagnosed with a glioma and 1,716 control subjects randomly selected from general practitioner lists from five areas in the United Kingdom. Exposure was measured using the number of years from first regular use of a phone until diagnosis or equivalent reference date for controls, lifetime years of regular use, lifetime cumulative use (hours), and lifetime cumulative number of calls. For participants who had used mobile phones for more than ten years, usage was stratified to heavy (113 hours) and light use (<113 hours).

Overall, no association was found between having a glioma and having used mobile phones (odds ratio [OR] 0.94; 95% confidence interval [CI], 0.78 – 1.13). Further analysis found no relation for glioma or glioma type (high vs low grade) and time since first use, lifetime years of use, or cumulative number of calls and hours of use. The researchers did report a significant OR of 1.24 (95% CI, 1.02 – 1.52) for a tumour ipsilateral to the side of phone use. However, this finding was counterbalanced by a reduced OR for contralateral use (0.75; 95% CI, 0.61 – 0.93), suggesting a possibility of recall bias among cases. The subgroup that reported using analog phones, which use higher power than digital mobile phones, was analysed separately, but no significant ORs were found for any of the exposure metrics utilised in the study.

Although individual case-control studies have found associations between glioma and mobile phone use for

specific variables such as development of ipsilateral high-grade astrocytoma[5] and rural versus urban use,[6] these findings have not been replicated by subsequent research. Despite the limitations inherent to the case-control design, the weight of evidence argues against a significant association between developing brain tumours and having a history of mobile phone use.

1. Muscat JE, Malkin MG, Thompson S, et al. Handheld cellular telephone use and risk of brain cancer. JAMA 2000;284:3001-3007. [LOE 3b]
2. Inskip PD, Tarone RE, Hatch EE, et al. Cellular telephone use and brain tumors. N Engl J Med 2001;344:79-86. [LOE 3b]
3. Christensen HC, Schuz J, Kosteljanetz M, et al. Cellular telephones and risk for brain tumors: a population-based, incident case-control study. Neurology 2005;64:1189-1195. [LOE 3b]
4. Lonn S, Ahlbom A, Hall P, Feychting M; for the Swedish Interphone Study Group. Long-term mobile phone use and brain tumor risk. Am J Epidemiol 2005; 161:526-535. [LOE 3b]
5. Hardell L, Mild KH, Carlberg M. Further aspects on cellular and cordless telephones and brain tumors. Int J Oncol 2003; 22:399-407. [LOE 3b]
6. Hardell L, Carlberg M, Hansson Mild K. Use of cellular telephones and brain tumor risk in urban and rural areas. Occup Environ Med 2005; 62:390-394. [LOE 3b]

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Bandolier Knowledge. In this section of the website, Bandolier collects good quality evidence under a variety of different headings. They search for systematic reviews of treatments, of evidence about diagnosis, epidemiology or health economics, and abstract it.

Go to http://www.jr2.ox.ac.uk/bandolier

Tricyclic antidepressants

Dear bpac,
Many thanks for your report on antidepressants prescribed to elderly people.

Please don't think for one moment that I treat depression in the elderly with TCA's. If I use TCA's it is for the treatment of insomnia for people waking up in the early morning hours. TCA's appear to be well tolerated in a very low dose (10–20 mg) even by the elderly. I also use TCA's in a moderate dose, up to 50mg, for chronic pain syndrome mostly for younger or middle aged people and I have tried it in a low dose to help people with smoking cessation.

I think it is well known that the treatment of depression with TCA in any age group has long become obsolete since the SSRIs have been developed. Apart from the well known side effects I still remember the suicide attempts with TCA we used to see many years ago when I was a senior medical registrar.

Runa Rao
GP, Tauranga

Many other GPs also told us that they are prescribing TCAs in elderly people for conditions other than depression — usually for neuropathic pain. TCAs can be associated with significant toxicity in overdose and this may influence prescriber choice. TCAs are an effective medication and can be used appropriately for several indications. However for depression in elderly people, consider an SSRI first.

The purpose of the prescribing report was to highlight the fact that if a TCA is prescribed, nortriptyline is the best choice for an elderly person as it has less sedative and anticholinergic effects than other TCAs.

Current guidance for missed combined oral contraceptive pills

Dear bpac,
Leaflets from different contraceptive pill packets contain differing advice regarding missed pills. What is the currently recommended advice for missed pills?

GP, Dunedin

Missing combined oral contraceptive pills

The New Zealand Family Planning Association (FPA) developed guidance for missed pills in 2006. Their advice is:
Missed one pill:

- The missed pill should be taken as soon as it is remembered and then carry on taking remaining pills as usual. This may mean taking two hormone pills together. No additional precautions are required.
- Consider emergency contraception if the missed pill was from the first seven days of the pack and the woman has had unprotected intercourse in the previous pill free interval. The risk of pregnancy is greatest when pills are missed at the beginning of the pack, extending the pill-free week, as efficacy may be reduced.

Missed two pills within a seven day period:

- An additional contraceptive method is required or intercourse should be avoided until seven active pills have been taken.
- Consider emergency contraception if sexual intercourse has occured before the seven active pills have been taken.

- If missed pills are in the week before inactive tablets/ pill-free week, the inactive pills/pill-free week should be missed and the next pack started after the active pills in the current pack are finished.

Vomiting and diarrhoea for more than 24 hours requires an additional contraceptive method until seven active pills have been taken. This may require skipping the pill-free week/inactive pills.

Missing progestogen only pills

If a progestogen only pill has been missed by more than three hours (or more than twelve hours for Cerazette), the missed pill should be taken as soon as possible. An additional contraceptive method is required or intercourse should be avoided until two days of pills have been taken. This is also required if a women vomits within three hours of taking a pill or if she has diarrhoea. Emergency contraception may be required if unprotected intercourse occurs in these two days.[1]

See page 23 for information on managing drug interactions with oral contraceptives e.g. antibiotics.

Reference:

1. National Prescribing Service Newsletter. Hormonal contraceptives: tailoring for the individual. Available from: http://www.nps.org.au/resources/NPS_News/news54/news54.pdf. Accessed February 2008.

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