Medicines Adverse Reactions Committee

Meeting date	**14 September 2017**	Agenda item	3.2.3
Title	**Risks of severe depression, anxiety and suicidal ideation with hormonal contraceptives**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice
Active constituents	**Medicines**	**Sponsors**	**Funding**
ethinylestradiol/levonorgestrel	Ava 20ED, 30ED	Teva Pharma	Y
	Levlen ED; Microgynon 20 ED, 30 ED, 50 ED	Bayer	Y Microgynon 50 ED only
	Loette, Monofeme	Pfizer	
ethinylestradiol/norethisterone	Brevinor 1 21 Day, 1 28 Day, 21; Norimin	Pfizer	Y
ethinylestradiol/cyproterone	Diane 35-ED	Bayer	
	Estelle-35, -35 ED	Douglas	
	Ginet	REX	Y
ethinylestradiol/desogestrel	Marvelon 28; Mercilon 28	MSD	Y partial subsidy
ethinylestradiol/ drospirenone	Yasmin; Yaz	Bayer	
ethinylestradiol/etonorgestrel	NuvaRing	MSD	
estradiol valerate/dienogest	Qlaira	Bayer	
desogestrel	Cerazette	MSD	
levonorgestrel	Jadelle subcutaneous implant	Bayer	Y
	Mirena IUD; Jaydess IUD	Bayer	Y Mirena IUD only with special authority
	Levosert IUD	Allergan	
	Microlut	Bayer	Y partial subsidy
medroxyprogesterone	Depo-Provera	Pfizer	Y
norethisterone	Noriday	Pfizer	Y
Previous MARC meetings	This has not been discussed previously		
Schedule	Prescription medicines except for ethinylestradiol/levonorgestrel and ethinylestradiol/norethisterone which can be supplied by a pharmacist if they have completed a Pharmacy Council and Pharmaceutical Society of New Zealand approved training programme.		
Advice sought	**The Committee is asked to advise:** – On the strength of the evidence for an association between hormonal contraceptives and severe depression, anxiety and suicidal ideation. – Whether updates to data sheets are necessary. – If this topic requires further communication other than MARC's Remarks in *Prescriber Update.*		

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1.0 PURPOSE

Medsafe recently reviewed information on the risk of suicidal ideation with the oral contraceptive containing cyproterone/ethinylestradiol. Although cyproterone/ethinylestradiol can be used as oral contraception, it is not recommended in women solely for contraception. It is possible that suicidal ideation occurs due to the conditions (eg, acne, polycystic ovary syndrome) that cyproterone/ethinylestradiol is used to treat rather than an adverse effect of treatment. Therefore, the scope of the review was widened and this paper summarises information on the risks of severe depression, anxiety and suicidal ideation with hormonal contraceptives. Excluded from this review are emergency contraceptive pills, and postnatal depression.

2.0 BACKGROUND

2.1 Hormonal contraceptives [1]

2.1.1 Combined hormonal contraceptives

Combined hormonal contraceptives (CHCs) contain an oestrogen and progestogen and are available as **oral tablets** or a **vaginal ring**. The majority of combined oral contraceptives (COCs) contain ethinylestradiol as the oestrogen component but estradiol is also used. The ethinylestradiol content of COCs ranges from 20 to 50 micrograms.

The progestogens desogrestrel, drospirenone and gestodene (in combination with ethinylestradiol) may be considered for women who have adverse effects (such as acne, headache, depression, breast symptoms and breakthrough bleeding) with other progestogens. Drospirenone, a derivative of spironolactone, has anti-androgenic and anti-mineralocorticoid activity.

The oral contraceptive containing ethinylestradiol/cyproterone has slightly different indications. It is indicated as oral contraception in women requiring treatment for androgen-dependent diseases including acne, and for the relief of symptoms of polycystic ovary syndrome (PCOS). It is not recommended in women solely for contraception.

2.1.2 Progestogen-only contraceptives

Oral: These contain either desogestrel, levonorgestrel or norethisterone. There is insufficient clinical trial evidence to compare the efficacy of oral progestogen-only contraceptives with each other or with combined hormonal contraceptives. Progestogen-only contraceptives offer a suitable alternative to combined hormonal contraceptives when oestrogens are contraindicated.

Injectable: Medroxyprogesterone acetate is a long-acting progestogen given by intramuscular injection. It is as effective as combined oral contraceptives.

Implant: The levonorgestrel-releasing implant is a highly effective long-acting contraceptive. It consists of two flexible rods which are inserted subdermally into the lower surface of the upper arm. It provides contraception for up to 5 years.

Intra-uterine: Intra-uterine devices (IUDs) release levonorgestrel directly into the uterine cavity. They may be a contraceptive method of choice for women who have heavy periods.

2.2 Depression

Epidemiology [2]

In the 2011/2012 New Zealand Health Survey, 14.3% of New Zealand adults (>500,000 people) had been diagnosed with depression at some time in their lives. These rates were significantly higher amongst women than men (17.9% vs 10.4%). The highest rates were amongst women aged 35–44 years (21%).

Risk factors

There are many factors that increase a person's vulnerability to depression [3]:

- Stressful events like a relationship break-up or financial trouble
- A family history of depression
- Physical illness such as a stroke or heart attack
- Stressful or traumatic events in childhood can lead to depression later in life
- Certain medicines can cause depression in some people
- Social isolation.

Major depression occurs more often in patients with specific risk factors. These multiple, interacting factors constitute three broad pathways for developing the illness [4]:

- Internalising factors: Genetics, neuroticism, low self-esteem, early-onset anxiety disorder, past history of major depression
- Externalising factors: Genetics, substance misuse, conduct disorder
- Adversity: Trauma during childhood or adulthood, stressful life events in past year, parental loss, low parental warmth, history of divorce, marital problems, low social support, low education.

Symptoms [5]

The main symptoms of depressive disorders are lowering of mood, reduction of energy and decrease in activity. Loss of appetite and weight, sleeping disorders especially waking up very early in the morning, and loss of libido often occur in patients with depressive disorders. Concentration and self-esteem may be reduced; patients might feel guilty and worthless. According to common definitions, dysthymia, acute stress reactions as well as adjustment disorders should be distinguished from the term "depressive episode".

Major depressive disorder [6]

Unipolar major depression (major depressive disorder) is diagnosed in patients who have suffered at least one major depressive episode and have no history of mania or hypomania. A major depressive episode is a period lasting at least two weeks with five or more of the following symptoms: depressed mood, anhedonia, insomnia or hypersomnia, change in appetite or weight, psychomotor retardation or agitation, lower energy, poor concentration, thoughts of worthlessness or guilt, and recurrent thoughts about death or suicide.

Reproductive and hormonal influences [7]

Reproductive events have an influence on several features in a woman's life including psychological wellbeing and mental health. Many psychiatric disorders, in particular mood and anxiety disorders, are more common in women than in men especially after puberty. Their onset and relapse are often related to the physiological cyclic nature of the menstrual cycle as well as to reproductive events like pregnancy, postpartum state and transition to menopause. This evidence suggests a possible influence of gonadal hormones on mental health.

Oestrogens, progesterone and their metabolites are known to exert a variety of effects on the central nervous system. These hormones are involved in the process of brain sexual differentiation, as well as in neuroprotection and modulation of serotoninergic, noradrenergic and dopaminergic systems.

Premenstrual tension syndrome (PMT) and premenstrual dysphoric disorder (PMDD)

Monthly occurring depressive symptoms may be part of premenstrual tension syndrome (PMT) [5]. Premenstrual dysphoric disorder (PMDD) is the more severe variant of PMT. Both are characterised by the presence of physical and/or behavioural symptoms that occur repetitively in the second half of the menstrual cycle and often during the first few days of menses [8].

The symptoms of PMT or PMDD are severe enough that they interfere with some aspects of the woman's life (eg, family, social, work etc.). The most common physical manifestation is abdominal bloating. Breast tenderness and headaches are also common.

PMDD can be differentiated from PMT by the presence of at least one affective symptom such as mood swings, irritability and/or depression [8]. Premenstrual symptoms are common affecting up to 75% of women with regular menstrual cycles. Clinically significant PMT occurs in 3–8% of women while PMDD affects about 2% of women [8]. The prevalence of PMT in the population has been overestimated (as high as 80%) due to failure of applying strict inclusion criteria [8].

A clear distinction between PMDD and depression is not always clear. Some symptoms such as depressed mood, feelings of hopelessness, decreased interest in usual activities, concentration difficulties, lack of energy, change in appetite, hypersomnia or insomnia are included in measures for both disorders. Irritability has been described as a more prominent symptom in women with PMT or PMDD than depressed mood. Differences in the dysregulation in the stress axes in women with PMDD and in women with current or past depressive disorders also suggest the two disorders to be distinct. In a longitudinal population-based twin study, it was suggested that genetic and environmental risk factors of premenstrual symptoms and major depression are not closely associated [9]. It appears that premenstrual symptoms are only influenced by familial-environmental factors to a small degree or not at all [9].

Both genetic and environmental factors play a role in the development of premenstrual symptoms. Preliminary evidence suggests that risk for PMDD is associated with genetic variation in *ESR1*, the oestrogen receptor alpha gene [8]. Other possible risk factors include lower education, smoking and a history of traumatic events or anxiety disorder [8]. In the normal menstrual cycle, cyclic fluctuations in luteal phase oestrogen and progesterone concentrations cause marked changes in neurotransmitters, most notably the serotonin system. Women with PMT/PMDD have normal concentrations of serum oestrogen and progesterone but they appear to have an abnormal neurotransmitter response (in particular, serotonin) to luteal phase hormonal changes [8].

Combined hormonal contraceptives

Historically, the use of combined hormonal contraceptives has been associated with depression and adverse mood effects in a subset of women [10]. In reviews prior to 1980, high rates of psychological side effects are described with increases in depressive symptoms ranging from 20% to 50% [11, 12]. However, much of this literature comes from a time when hormone doses were considerably higher causing somatic side effects that may have affected mood as well.

Since then, many formulations of combined hormonal contraceptives with lower dosage have been introduced that maintain contraceptive efficacy while decreasing unpleasant side effects [10]. The options for combined hormonal contraceptives have also expanded to include non-oral forms. However, psychological side effects continue to be a contributing factor to non-compliance [10].

Precise estimates of adverse mood symptoms with combined oral contraceptives are not available due to the lack of large placebo-controlled trials [13]. Adverse mood symptoms and somatic symptoms are most pronounced during the pill-free interval of treatment cycles, but whether extended regimens would be more favourable is not known [13]. Those with anti-androgenic progestogens such as drospirenone and desogestrel appear more favourable in terms of mood symptoms than progestogens with a more androgenic profile [13].

Yaz (ethinylestradiol 20 mcg + drospirenone 3 mg) is also indicated for treatment of symptoms of premenstrual dysphoric disorder (PMDD) in women who have chosen oral contraceptives as their method of birth control [14]. Yaz has not been evaluated for treatment of premenstrual tension syndrome (PMT).

Yaz in the treatment of PMDD in women seeking contraception has been investigated in two randomised, double-blind, placebo-controlled trials [15, 16]. Both studies used the Daily Record of Severity of Problems scale which was specifically developed to aid in the diagnosis and evaluation of PMDD. Efficacy was assessed by change from baseline during treatment using a scoring system based on the first 21 items. In both trials, women who received Yaz had statistically significantly greater improvement in their scores.

The 2012 Cochrane review of all randomised controlled trials with Yaz for effect on premenstrual symptoms concluded that Yaz may help treat premenstrual symptoms in women with severe symptoms, that is, PMDD [17]. Five trials with a total of 1920 women were included in the review. Two placebo-controlled trials of women with PMDD showed less severe premenstrual symptoms after three months with Yaz than with placebo (MD -7.92; 95% CI -11.16 to -4.67), greater mean decreases in impairment of productivity, social activities and relationships. Side effects common with the use of drospirenone were nausea, intermenstrual bleeding and breast pain.

Progestogen-only contraceptives

Women taking progestogen-only contraceptives do not appear to experience more depressive symptoms or mood changes than women on other hormonal contraceptives and they may experience slightly less depression than women using no contraception [18].

A retrospective cohort trial compared 298 women on progestogen-only contraception with 6356 women on other or no contraception to examine the association between contraception use and depressive symptoms [19]. When surveyed with the Center of Epidemiological Studies Depression Scale, women on progestogen-only contraception demonstrated significantly lower levels of depressive symptoms compared with women using low-efficacy contraception (early withdrawal, spermicides, contraceptive films) or no contraception (mean deviation -1.3; 95% CI -2.4 to -0.2). No significant difference was seen in depression scores when compared with women on other forms of hormonal contraception (mean deviation -0.3; 95% CI -1.2 to 0.6).

A cross-sectional population-based trial conducted by survey in Finland in 1997, 2002 and 2007 investigated the link between contraception and mood symptoms. It included 759 women using progestogen-only levonorgestrel-releasing intrauterine devices (LNG-IUD) and 7036 women on other forms of contraception or none [7]. Current LNG-IUD users vs non-users had no significant difference in diagnosis of depression as assessed by asking patients if they had been diagnosed with or treated for depression in the previous year of contraception (8% vs 7.3%; $p > 0.05$); depressive symptoms in the previous year (24% vs 26%; $p > 0.05$) or psychological illness (1.9% vs 2.5%; $p > 0.05$). LNG-IUD users reported significantly less anhedonia than non-users in the previous year (19% vs 22%; $p < 0.05$).

A multicentre prospective cohort trial analysed the effect of the levonorgestrel implant on mood in 267 women followed for 2 years by evaluating depressive symptoms reported from the Mental Health Inventory, a 6-item questionnaire scored 0 to 24 [20]. The women demonstrated a significant increase in depressive symptom scores from 7.9 at baseline to 8.8 ($p = 0.01$). The 62 women who experienced a decrease in relationship satisfaction exhibited a significant increase in depressive symptoms (6.7 to 10; $p = 0.001$) compared with the 156 women who reported an improvement or no change in relationship satisfaction (7.8 to 8.2; $p = 0.30$).

Polycystic ovary syndrome (PCOS)

Contraceptives containing ethinylestradiol/cyproterone are indicated for the relief of symptoms of polycystic ovary syndrome (PCOS). Several studies have shown that women with PCOS are more likely to experience depressive symptoms than healthy women [21-24]. There have also been reports that PCOS in adult women is associated with increased anxiety, eating disorders, obsessive-compulsive symptoms and reduced quality of life but findings have been inconsistent [25-33].

Factors that may be associated with depression and poorer quality of life in PCOS women include higher BMI, androgen excess symptoms and subfertility, but data examining these possible relationships are sparse and conflicting [26, 27].

The rate of depression in PCOS ranges from 14 to 67% [24, 34] and the prevalence of anxiety is reported to be as high as 34 to 57% [23, 35]. An 8.1-fold increased risk of depression in patients with PCOS compared with healthy women (28.6 vs 4.7%) has also been found [36].

An observational study conducted in New Zealand investigated whether adolescents with PCOS are more depressed than adolescent girls in the community and examined factors associated with depression [37].

102 girls aged 14 to 19 presenting for clinical assessment fulfilling the Rotterdam consensus for PCOS were compared with 1349 girls from a school-based survey of New Zealand youth. This study found that clinically significant depression in adolescent girls with PCOS was not increased compared with the community sample (OR 1.3; 95% CI 0.7–2.7, p = 4.2). Within the PCOS cohort, depression was correlated with increased BMI and possibly acne.

Comments:

Depression is a complex condition influenced by both genetic and environmental factors.

It is difficult to clearly distinguish depression from changes in mood, symptoms of PMT/PMDD and acute stress reactions. In addition, some studies have found women with polycystic ovary syndrome are more likely to experience depressive symptoms than women without polycystic ovary syndrome. This is particularly relevant for hormonal contraceptives that have additional indications for use in polycystic ovary syndrome or PMT/PMDD.

The risk of depression with CHCs was first reported many years ago and the products and formulations available were quite different to those available now. It is not clear whether the products and formulations available now are more or less likely to be associated with depression compared to older products and formulations.

2.3 Anxiety

Occasional anxiety is part of normal life. However, people with anxiety disorders frequently have intense, excessive and persistent worry and fear about everyday situations. Anxiety is a distressing, unpleasant emotional state of nervousness and uneasiness and its causes are less clear. Anxiety is often accompanied by physical changes and behaviours similar to those caused by fear. Some degree of anxiety is adaptive and can help people prepare and practice so that their functioning is improved. However, beyond a certain level, anxiety causes dysfunction and undue distress. At this point, it is maladaptive and considered as a disorder.

Generalised anxiety disorder (GAD) is characterised by excessive and persistent worrying that is hard to control, causes significant distress or impairment and occurs on more days than not for at least 6 months [38]. Other features include psychological symptoms of anxiety such as apprehensiveness and irritability and physical (or somatic) symptoms of anxiety such as increased fatigue and muscular tension [38]. Major depression and other anxiety disorders are common comorbidities of GAD [38].

Epidemiology

In the 2011/2012 New Zealand Health Survey, 6.1% (more than 200,000 people) had been diagnosed with anxiety disorders at some time in their lives. These included generalised anxiety disorder, phobias, post-traumatic stress disorder and obsessive-compulsive disorder [2]. Rates were significantly higher amongst women than men (7.7% vs 4.4%) [2]. The highest rates were amongst women aged 25–54 years (9%).

Comorbidity with major depression or other anxiety disorders has been observed in the majority of cases of GAD [38]. Patients with comorbid major depression and GAD tend to have a more severe and prolonged course of illness and greater functional impairment [38]. The presence of comorbid major depressive episodes is associated with a poorer prognosis in patients with GAD [38].

Pathogenesis [38]

Genetic factors appear to predispose individuals to the development of GAD, though data from twin studies have been inconsistent. GAD shares a common heritability with major depression and with the personality trait of “neuroticism”. Adversity and undesirable life events can exacerbate symptoms of GAD. Neuroimaging and other studies suggest the symptoms of GAD are accompanied by an enhanced emotional responsiveness in fear-related brain circuits.

Clinical manifestations [38]

Although excessive and persistent worrying is widely regarded as the pathognomonic feature of GAD, most patients present with other symptoms relating to hyperarousal, autonomic hyperactivity and muscle tension. Many complain of poor sleep, fatigue and difficulty relaxing. Headaches and pain in the neck, shoulders and

back are commonly reported. It is common for patients with these symptoms to present to health professionals repeatedly, with pressing but long-standing concerns that prove to be medically unexplained.

GAD tends to run either a chronic course fluctuating in severity over time, or an episodic course with some intervening periods of relative wellbeing. Comorbid GAD and major depression is more impairing and has a worse prognosis.

Differential diagnosis

It is important to exclude medical conditions with similar presentations when evaluating a patient for a suspected anxiety disorder. These include endocrine conditions (eg, hyperthyroidism), cardiopulmonary conditions (eg, arrhythmia), and neurological diseases (eg, temporal lobe epilepsy or transient ischaemic attacks). The use of substances such as caffeine, decongestants or substance withdrawal may also present with similar symptoms and should be ruled out.

Distinguishing GAD from major depression and dysthymia is probably the most difficult part of the disorder's differential diagnosis as the conditions share features such as an insidious onset, protracted course, prominent dysphoria and anxiety symptoms [38]. Individuals with depression tend to brood self-critically on previous events and circumstances whereas patients with GAD tend to worry about possible future events [38].

2.4 Suicidal ideation

Epidemiology

It is estimated that there are 10 to 40 non-fatal suicide attempts for every completed suicide [39]. This number increases to 100 to 200 for adolescents [39]. The prevalence of suicidal thoughts, plans, gestures and attempts does not appear to have changed significantly in the US between the early 1990s and the early 2000s [39]. In 2004, 19% of suicide victims had a history of prior attempts [39].

In 2014, 504 people died by suicide in New Zealand, which equates to an age-standardised rate of 10.7 per 100,000 [40]. The highest rate of suicide was among people aged 25–44 years (16.2 per 100,000) [40]. There were 378 male suicides and 126 female suicides (16.4 per 100,000 and 5.3 per 100,000 respectively). For every female suicide there were 3.1 male suicides.

Over the 10 year period 2005–2014, the rate of suicide has remained relatively stable year to year [40].

Risk factors

Protective and risk factors for suicide are summarised in Table 1.

Table 1: Protective and risk factors for suicide [41]

Protective factors	Risk factors

• Having access to community support and health resources, such as:
  ◦ affordable healthcare
  ◦ good schooling
  ◦ supportive community groups or churches
  ◦ appropriate social services
• Being connected socially, such as:
  ◦ having healthy friendships
  ◦ caring family relationships
• Having the skills to cope with life's difficulties, such as:
  ◦ being resilient and able to 'bounce back'
  ◦ having a positive outlook; knowing things will get better
  ◦ being able to think and reason clearly
	• Mental health issues, such as:
	  ◦ depression
	  ◦ post-traumatic stress disorder (PTSD)
	• Being exposed to some sort of trauma, for example:
	  ◦ a disaster
	  ◦ family violence
	  ◦ abuse
	• Having a lack of social support, for example:
	  ◦ living alone
	  ◦ being socially isolated
	• Experiencing stressful life events, for example:
	  ◦ chronic pain
	  ◦ addiction
	  ◦ discrimination
	  ◦ bullying
	  ◦ relationship conflict
	  ◦ job loss or financial problems

2.5 Data sheets

Information in New Zealand data sheets is summarised below. This has been compared with data sheets in the UK. Where differences exist, these have been highlighted.

2.5.1 Combined hormonal contraceptives

Oral (ethinylestradiol/levonorgestrel or ethinylestradiol/norethisterone): All data sheets list depressed mood and altered mood as common undesirable/adverse effects.

Some data sheets (Loette, Monofeme, Brevinor) also include information on depression in the warnings and precautions section. The exact wording varies but the intent is the same:

> *Oral contraceptives may cause depression. Patients with a history of depression should be carefully observed and the drug discontinued if depression recurs to a serious degree. Patients becoming significantly depressed while taking oral contraceptives should stop the medication and use an alternative method of contraception in an attempt to determine whether the symptom is drug-related.*

Oral (ethinylestradiol/cyproterone): All data sheets (Ginet, Diane, Estelle) list depressed mood and altered mood as common undesirable/adverse effects.

The Dianette UK SPC also includes:

> *Post-marketing reports of severe depression (including very rare reports of suicidal ideation or behaviour) in patients using Dianette have been received. However, a causal relationship between clinical depression and Dianette has not been established.*

Oral (ethinylestradiol/desogestrel): These data sheets (Marvelon, Mercilon) include depression as a relative contraindication. Depressed mood and mood altered are listed as common undesirable/adverse effects. There is also information on depression in the warnings and precautions section (as detailed above with additional information on using vitamin B6 if this is accompanied by a disturbance of tryptophan metabolism).

Oral (ethinylestradiol/drospirenone): Both data sheets (Yasmin, Yaz) list emotional lability and depression/depressive mood as common undesirable/adverse effects. The Yaz data sheet also includes information on premenstrual dysphoric disorder (PMDD) in the pharmacodynamic properties section:

> *The essential features of PMDD according to the Diagnostic and Statistical Manual-4th edition (DSM-IV) include markedly depressed mood, anxiety or tension, affective lability, and persistent anger or irritability. Other features include decreased interest in usual activities, difficulty concentrating, lack of energy, change in appetite or sleep, and feeling out of control. Physical symptoms associated with PMDD include breast tenderness, headache, joint and muscle pain, bloating and weight gain. In this disorder, these symptoms occur regularly during the luteal phase and remit within a few days following onset of menses. The disturbance markedly interferes with work or school, or with usual social activities and relationships with others. Diagnosis is made by healthcare providers according to DSM-IV criteria, with symptomatology assessed prospectively over at least two menstrual cycles. In making the diagnosis, care should be taken to rule out other cyclical mood disorders.*

Oral (estradiol/dienogest): The Qlaira data sheet lists depression/depressed mood, mental disorder and mood change as uncommon undesirable/adverse effects. Additional psychiatric disorders are also listed in the Qlaira data sheet including affect lability, aggression, anxiety, dysphoria, nervousness and emotional disorder.

Vaginal ring (ethinylestradiol/etonogestrel): The NuvaRing data sheet lists depression and emotional lability as common undesirable/adverse effects.

Comments:

All combined oral contraceptive data sheets include depressed mood and/or altered mood as undesirable/adverse effects. Some also include information in the warnings and precautions section. None of the data sheets include any information on suicidal ideation. The UK SPC for ethinylestradiol/cyproterone includes information on severe depression including suicidal ideation or behaviour.

2.5.2 Progestogen-only contraceptives

Oral (desogrestrel): The Cerazette data sheet lists mood altered as a common undesirable/adverse effect. There is no information on depressed mood or depression.

The Cerazette UK SPC lists mood altered and depressed mood as common undesirable/adverse effects.

Oral (norethisterone): The Noriday data sheet lists mental depression as an undesirable/adverse effect. There is also information on carefully observing patients with a history of depression in the warnings and precautions section.

Oral (levonorgestrel): The Microlut data sheet lists depressed mood as a rare undesirable effect.

Injectable (medroxyprogesterone): The Depo-Provera data sheet lists depression, insomnia and nervousness as undesirable/adverse effects. There is also information on carefully monitoring patients with a history of treatment for clinical depression in the precautions section.

Implant (levonorgestrel): The Jadelle data sheet lists mood changes and depression as common undesirable/adverse effects. It also includes information on careful monitoring in women with a history of depression in the warnings and precautions section.

Intra-uterine (levonorgestrel): The data sheets (Mirena, Jaydess) lists depressed mood/depression and nervousness as common adverse reactions reported in clinical trials. Altered mood is listed as uncommon. There is no published data sheet for Levosert.

Comments:

All data sheets list depressed mood or altered mood as undesirable/adverse effects. Some also include information on carefully monitoring patients with a history of depression.

3.0 SCIENTIFIC INFORMATION

3.1 Published literature

Studies have been conducted investigating the risks of depression and mood disorders with hormonal contraceptives. These are presented below. No studies were identified that specifically studied the occurrence of suicidal ideation in users of hormonal contraceptives.

3.1.1 Review articles

Bottcher et al 2012 — Hormonal contraception and depression: A survey of the present state of knowledge [5]

The authors performed an analysis of existing studies to examine a possible correlation between depression and the use of hormone-based contraceptives.

Data on this topic are limited. At least two confounding variables influence the analysis of the available data and make it difficult to draw firm conclusions: the inconsistent use of the term “depression” and the large number of combined contraceptives which vary in their composition.

In many publications it is not clear which classification system for depression was used. For example, a major depression is not equivalent to negative mood changes, tension, irritability, anxiety or sadness. Some

of these terms refer to symptoms of premenstrual syndrome which should be clearly distinguished from a major depression. In addition, criteria of classification have changed over the years (70s to now). The composition of hormonal contraceptives has also changed dramatically with the dose of ethinylestradiol consistently reduced over the years.

The psychological element as well as the anticipation of possible side effects, and a possible change in sexual behaviour caused by taking oral contraceptives might influence certain feelings like mood changes and anxiety, for example.

The influence of different gestagens on the frequency and intensity of side effects should not be underestimated. Hormonal contraceptives containing only gestagens might lead to depressive symptoms or major depression more frequently than combined oral contraceptives. The authors are of the opinion that progestogen-only contraceptives may have a negative influence on mood, whereas oestrogens may have positive effects on depressive symptoms.

The association between the use of oral contraceptives and depression is not clear. The authors found that depression is not a common side effect of hormone-based contraceptives.

The authors conclude that individual, patient-based decisions with consideration of the individual history and predispositions are recommended when starting oral contraceptive. If depressive symptoms or mood changes occur, decisions regarding discontinuation or medication change need to be made on an individual basis.

Comments:
This article is helpful in summarising the pitfalls and difficulties in examining the relationship between depression and hormonal contraception.

Poromaa et al 2012 — Adverse mood symptoms with oral contraceptives [13]

This overview addressed the following questions: How common are adverse mood symptoms in contraceptive users? During which part of the treatment cycle are adverse mood symptoms most pronounced? How frequently are adverse mood symptoms drug-related? Are there any contraceptives with a more beneficial profile with respect to mood symptoms? Are there sub-groups of women where combined oral contraceptives (COCs) may have particularly positive mood effects?

The assessment of adverse mood symptoms during COC use represents a scientific challenge and various study designs have been used to elucidate this issue. In prospective trials the frequency of women who report deteriorated mood or deteriorated emotional wellbeing has varied between 4 and 10% but these figures are substantially higher in retrospective studies [42, 43]. However, not all adverse mood symptoms experienced by COC users are drug-related. Psychiatric history, personality traits, interpersonal relationships and socioeconomic factors are also likely to contribute to adverse mood symptoms which are often attributed to COC treatment [44, 45]. In addition, age at first onset of a depressive episode or anxiety disorder often coincides with a time in life when COC use is very prevalent [46-48].

Although the available placebo-controlled trials have been mostly positive (no differences or improvements in mood), studies have been conducted in sterilised women, in women with dysmenorrhoea and in women with premenstrual dysphoric disorder (PMDD) [15, 16, 49-52]. Based on placebo-controlled studies and longitudinal epidemiological studies, it can only be hypothesised that prevalence rates suggested in non-controlled trials and epidemiological studies are overestimated.

It appears that COCs with anti-androgenic progestogens such as drospirenone (DRSP) and desogestrel are more favourable in terms of mood symptoms than progestogens with a more androgenic profile [43, 53-56]. There is available data that lower doses of ethinylestradiol (EE) could be more beneficial [56] which is also supported by data from women with PMDD where 20 µg EE-DRSP was superior to placebo whereas 30 µg EE-DRSP was not [15, 16, 52]. However, these COC treatments may not be readily comparable as a shorter hormone-free interval may have contributed to the success of the 20 µg EE-DRSP compound.

Adverse mood symptoms and somatic symptoms are most pronounced during the pill-free interval of treatment cycles [43, 57, 58] and studies evaluating mood across different treatment phases have most often reported positive effects in the premenstrual and menstrual phases [43, 53, 59, 60].

Certain sub-groups of women such as those with PMDD may particularly benefit from COC use. Results in women with major depression are interesting and a clear shift from the perspective of the 1960s where COCs were thought to increase the risk of major depression. However, although open-label studies are promising, they may also represent regression towards the mean in women severely disabled by their depression.

Comments:

As with the article by Bottcher et al, this article is a good summary of the challenges on this topic including discussion of PMDD and use of anti-androgenic progestogens. However, the focus was on adverse mood symptoms rather than depression.

Schaffir et al 2016 — Combined hormonal contraception and its effects on mood: A critical review [10]

Adverse mood changes are sometimes cited as a reason for discontinuing combined hormonal contraception (CHC). A systematic review of recent literature (last 30 years) was undertaken to characterise the nature of these side effects and identify characteristics that might predispose women to such effects. The heterogeneity of studies reviewed precluded performing a meta-analysis.

Table 2 summarises studies that compare hormonal contraceptive users compared with non-users. Table 3 summarises studies that compare one combined hormonal contraceptive with another.

The research literature on this topic is limited by a lack of prospective studies, a variety of measurements of mood and a consolidation of many disparate types of contraceptives studied together in a single cohort. Common themes that emerge from review of these papers include:

- Most women using combined hormonal contraception demonstrate no effect or a beneficial effect on mood, with a low incidence of adverse effects
- Contraceptives containing less androgenic progestogens may have fewer adverse effects on mood
- Continuous and perhaps non-oral dosing of combined hormonal contraceptives has the fewest mood effects
- Women with underlying mood disorders may be predisposed to mood effects but this may reflect factors related to choice of contraception rather than the mood disorder itself.

Inconsistent research methods and lack of uniform assessments make it difficult to make strong conclusions about which combined hormonal contraceptive users are at risk for adverse mood effects. Until more prospective data is available, clinicians should recognise that such effects are infrequent.

Comments:

The tables of relevant studies are useful in summarising the evidence. This study also primarily focused on adverse mood effects rather than depression.

Table 2: General comparisons of hormonal contraceptive users and non-users

Study	Study population	Study design	Outcome(s) measured	Contraceptive method	Finding	Comment
Graham et al. [6]	150 Scottish and Filipino women, all sterile or with sterile partners	Randomised controlled trial	BDI, mood self-report	Levonorgestrel combined pill versus levonorgestrel only pill versus placebo	Fewer depressive symptoms in progestin-only group; no difference between groups by third month	Only women in Scotland had more premenstrual mood changes in combined pill group
Keyes et al. [7]	6654 women between 25 and 34 years old	Prospective cohort	CES-D	Any HC versus non-HC versus no contraception	Fewer depressive symptoms in HC group	
Toffol et al. [8]	8000 Finnish women in longitudinal health study	Observational	BDI, GHQ-12, Diagnostic Interview	Comparison of various contraceptive methods	No difference between COC users versus non-users	Lower depression score over time of exposure with COC
Toffol et al. [9]	8586 Finnish women with average age 40	Observational	BDI	Comparison of various contraceptive methods	Current COC users demonstrated better mood than non-users	
Duke et al. [10]	9688 reproductive age Australian women	Observational	CES-D	Any COC	No difference between users and non-users	Number of women reporting depressive symptoms decreased over time exposed.
Svendal et al. [11]	498 women age 20–50 in osteoporosis study	Observational	Structured clinical interview	COC versus progestin-only contraceptives versus no contraception	Current COC users have lower likelihood of current mood disorder	Increased risk of mood disorder in the 33 women using progestin only
Oddens et al. [12]	1466 reproductive age German women	Observational	Mood self-report	COC versus other contraceptives	16% of women using COC experienced negative mood change	Higher percentage of negative mood change in users of condoms or natural family planning
Oinonen and Mazmanian [13]	129 university students	Prospective cohort	PANAS	COC starters versus long-time users versus non-users	Mean measurements of affect similar between groups	Users of triphasic COC had greater variability in positive affect across cycle
Berenson et al. [14]	608 women between 16 and 33 in study on bone mineral density	Prospective cohort	BDI, Zung Anxiety Instrument, PANAS	Low dose desogestrel COC versus DMPA versus non-users	Lower depressive scores and fewer mood swings in COC and DMPA groups than control	No differences in negative affect scores or anxiety
Almagor and Ben-Porath [17]	50 undergrad students and university technicians	Prospective cohort	Mood checklist	Any COC versus non-users	COC users experience more positive affect during cycle; no difference in negative affect	
Natale and Albertazzi [16]	62 young healthy women	Prospective cohort	Profile of mood states and VAS of mood	Any COC versus non-users	No significant difference in mood between users and non-users	
Marriott and Faragher [15]	65 healthy women	Prospective cohort	Moos menstrual distress questionnaire	Any COC versus non-users	No significant difference in psychological state between groups	
Kulkarni et al. [18]	58 healthy women	Prospective cohort	BDI, HAMD and MADRS	Any COC versus non-users	Mean depression scores significantly higher for COC group	

COC: combined oral contraceptive; HC: hormonal contraceptive; DMPA: depot medroxyprogesterone acetate; BDI: Beck Depression Inventory; CES-D: Center for Epidemiologic Studies Depression; PANAS: Positive and Negative Affect Schedule; HAMD: Hamilton Rating Scale for Depression; MADRS: Montgomery–Asberg Depression Rating Scale; GHQ-12: 12-item General Health Questionnaire.

Table 3: Studies that compare one combined hormonal contraceptive with another

Study	*n*	Study design	Outcome(s) measured	Contraceptive method	Finding	Comment
Akerlund et al. [20]	1000 women starting COC	Randomised prospective trial	Symptom checklist	20 mcg versus 30 mcg of EE combined with desogestrel	Higher depressive symptoms reported in 20 mcg estrogen group	
Greco et al. [21]	60 university students	Randomised prospective trial	BDI	Triphasic norgestimate COC with 25 mcg versus 35 mcg of EE	No significant difference in BDI scores	More improvement in premenstrual mood in 25 mcg group
Warner and Bancroft [22]	4112 women already using COC	Retrospective Questionnaire	'Peak mood and wellbeing'	Various COC: monophasic types compared with triphasic types	Fewer depressive symptoms inmonophasic group	Used non-validated psychometric. Most had mood 'trough' in premenstrual week
Bancroft and Rennie [23]	276 women with premenstrual syndrome	Observational	Symptom checklist	Monophasic versus triphasic COC	No difference in depression Triphasic COC users had most premenstrual negative mood symptoms	
Walker and Bancroft [24]	122 women with premenstrual syndrome	Observational	VAS of mood	Monophasic versus triphasic versus no OC	Mood decreased in all three groups as menses approached	
Coffee et al. [25]	114 healthy women starting COC	Prospective observational	Single-item mood scale; daily symptom report	Cyclic versus continuous regimen of 30 mcg EE/3 mg drospirenone pill	Less mood swings and depression with continuous regimen	Mood correlated with daily symptoms
Sabatini and Cagiano [26]	280 healthy women starting HC	Randomised trial	Side effects questionnaire	Levonorgestrel pill versus gestodene pill versus etonogestrel ring	COC groups noted more negative mood than ring	All groups noted depression decreased over time
Urdl et al. [28]	1489 healthy women age 18-45	Randomised trial	Questionnaire of 'emotional well-being'	Norelgestromin patch versus desogestrel pill	Emotional well-being greater in patch group	Emotional well-being correlated with physical well-being
Suceto et al., [29]	80 adolescents	Prospective observational	Brunel Mood Scale; Youth Quality of Life instrument	Norelgestromin patch versus levonorgestrel pill	No significant difference in mood side effects	Both groups with decreased premenstrual depression from baseline
Creinin et al. [30]	500 healthy women using COC	Randomised trial	Side effects questionnaire	Etonogestrel ring versus norelgestromin patch	No significant difference reported in mood swings	
Shahnazi et al. [31]	82 healthy women starting COC	Randomised prospective trial	PANAS	30 mcg EE pills with levonorgestrel versus desogestrel	Levonorgestrel pill group had fewer positive affect changes and more negative affect changes.	
Kelly et al. [33]	280 healthy women starting COC	Randomised prospective trial	MDQ and prospective questionnaire	30 mcg EE pill with either 3 mg of drospirenone or 150 mcg of levonorgestrel	Groups had similar scores of 'emotional well-being,'; drospirenone group had less negative affect in menstrual phase	
Deijen et al. [32]	370 women switching from other COC	Observational	Amsterdam Mood Questionnaire	30 mcg EE/75 mcg of gestodene versus any other COC	Women switching to gestodene COC from other COC showed improvements on ratings of depression, mood, and anxiety.	No reason given for switch or whether adverse mood effects present prior to switch
Santhawan and Taneepanichskul [34]	104 healthy women	Randomised prospective trial	MDQ WHAQ	Drospirenone COC versus levonorgestrel COC	Drospirenone group had significantly greater decrease in negative affect from baseline	Negative affect correlates with somatic symptoms
Borenstein et al. [35]	11260 women self-selecting Yasmin	Observational sponsored by manufacturer	MDQ Short form 12-HRQoL	30 mcg EE/3 mg drospirenone	Significant improvement in negative affect scores after 2 months	
Skrzypulec and Droszdol [36]	126 healthy women using COC	Observational	SF-36 Quality of life scale	30 mcg EE/3 mg drospirenone versus any other COC	Mental health domain scores higher in drospirenone group	
Witjes et al. [38]	3522 healthy women	Prospective observational	MDQ-C	EE/drospirenone pill versus 17B estradiol/nomegestrol acetate pill	Nomegestrol pill group had more improvement in negative affect scores	

COC: combined oral contraceptive; EE: ethinyl estradiol; BDI: Beck Depression Inventory; MDQ: Moos Menstrual Distress Questionnaire; WHAQ: Women's Health Assessment Questionnaire; HRQoL:Health-Related Quality of Life; VAS: Visual Analogue Scale; PANAS: Positive and Negative Affect Schedule; SF-36: Short Form 36 Health Survey.

Pagano et al 2016 — Safety of hormonal contraception and intrauterine devices among women with depressive and bipolar disorders: A systematic review [61]

The authors searched for articles published through January 2016 on the safety of using any hormonal contraceptive method among women with depressive or bipolar disorders, including those who had been diagnosed clinically or scored above threshold levels on a validated screening instrument. Outcomes included changes in symptoms, hospitalisation, suicide and modifications in medicine regimes such as increase or decrease in dose or changes in type of medicine.

Of 2376 articles, 6 met the inclusion criteria. None of the 6 studies found that hormonal contraceptives negatively influenced depressive or bipolar disorders. Four of these studies examined women with depression or women who scored above a threshold on a validated depression screening instrument, and all four found that combined oral contraceptive or oral contraceptive use was not associated with increased depressive symptoms compared with non-users [50, 62-64]. One study of women with bipolar disorder reported that oral contraceptive users did not have significant mood changes across the menstrual cycle, but that those not taking oral contraceptives did have significant mood changes [65]. Another study found that the frequency of psychiatric hospitalisations for women with bipolar disorder did not significantly differ between women using medroxyprogesterone (DMPA), levonorgestrel IUD, copper IUD or sterilisation [66].

Several limitations exist for this body of evidence. No standard definition or assessment of depressive and bipolar disorders or symptoms was used across studies. Of the four studies that used validated depression scales, each used a different scale and threshold level to classify participants as having the disorder or screening positive. Additionally, two of these studies determined thresholds from mean depression scores among study participants at baseline rather than recommended thresholds from published literature. Two studies did not specify the type of oral contraceptives examined and all five studies that examined oral contraceptives relied on self-report. One study misclassified women using hormone therapy as oral contraceptive users without stratifying findings. Additionally, the timing of oral contraceptive use relative to outcome measurement was not reported in two studies. Four studies did not consider potential confounders or establish baseline comparability between study groups and one did not report the specific confounders adjusted for during analyses. Due to these limitations, the RCT was rated as having poor quality [50], three of the prospective cohort studies were rated as having poor quality [63-65] and two of the prospective cohort studies were rated as having fair quality [62, 66].

The authors conclude that limited evidence from 6 studies found that oral contraceptives, levonorgestrel-releasing IUD and DMPA use among women with depressive or bipolar disorders was not associated with worse clinical course of disease compared with no hormonal method use.

Comments:

This review focused on women with depressive and bipolar disorders. The studies included in this review had similar limitations to studies studying depressive or adverse mood effects in women with no history of depressive and bipolar disorders who are using hormonal contraceptives.

3.1.2 Individual studies and case reports

Kulkarni 2007 — Depression as a side effect of the contraceptive pill [67]

The author reports a pilot study conducted in 58 women using well validated depression rating scales in a healthy population of women. This study explored the impact of using the combined contraceptive pill on mental state. An expert opinion is also included.

Of the 58 women, 26 were current users of combined oral contraceptives and the rest (32) were non-users and had not used a combined oral contraceptive for at least 2 months. Assessment tools included three depression rating scales: the Beck Depression Inventory (BDI); the Hamilton Rating Scale for Depression; and the Montgomery-Asberg Depression Rating Scale (MADRS). A clinician-rated assessment tool, the Global

Assessment of Functioning (GAF) Scale, was used to provide an overall measure of psychiatric symptoms and the level of social functioning.

The two groups were similar in terms of basic demographics. Analysis of variance showed that self-reported symptoms of depression were significantly higher among users than non-users (Table 4). GAF scores were significantly lower, suggesting greater social disability in users than non-users, although the mean scores of both groups were in the normal range. The mean scores on two of the three depression inventories (BDI, MADRS) for users suggested mild depression compared with the non-users group whose scores were normal. The results from this small study suggest that women using the combined oral contraceptive had more depressive symptoms both subjectively and objectively measured compared with non-users.

Table 4: Mean depression scores for combined oral contraceptive (COC) users and non-users

		Mean (standard deviation)	
Rating scale	COC	Non-COC	*p*
GAF*	75.6 (12.3)	85.1 (7.6)	0.001
MADRS‡	9.2 (7.3)	4.1 (3.8)	0.001
HAMD‡	10.0 (6.7)	5.2 (3.4)	0.001
BDI-II‡	9.7 (6.6)	5.9 (4.6)	0.011

*Higher scores indicate better social function.
‡Higher scores indicate worse depressive symptoms.
BDI: Beck depression inventory; COC: Combined oral contraceptive; GAF: Global assessment of functioning; HAMD: Hamilton rating scale for depression; MADRS: Montgomery–Asberg depression rating scale.

Expert opinion: Special care needs to be taken with the woman who has a history of depression or a strong family history of depression when prescribing an oral contraceptive. In addition, the specific disorder of 'late luteal dysphoric disorder' or 'premenstrual dysphoric disorder' appears to be related to decreases in circulating estradiol levels or to the cyclical variations in progesterone plus estradiol. Some women with these diagnoses find relief from their depressive symptoms by using the oral contraceptive to even out the fluctuations in the hypothalamic-pituitary-gonadal steroid production so in this instance, the regular use of active OC has an antidepressant effect.

Comments:

This pilot study included a small sample of women (n=58). The use of validated assessment tools is reassuring. Although the results suggest that users had more depressive symptoms than non-users, the authors' opinion includes a practical approach whereby consideration is made for women who may experience depressive symptoms as part of cyclic variations (eg, PMDD), and additional caution in women with a history of depression.

Duke et al 2007 — Is there an association between the use of oral contraception and depressive symptoms in young Australian women? [62]

This study explored the relationship between oral contraceptive use and the experience of depressive symptoms among a representative sample of young Australian women. The study sample was from the Australian Longitudinal Study on Women's Health. Analysis was confined to women in the youngest cohort who responded to Survey 2 which was conducted in 2000 (n=9688) when they were aged between 22 and 27 years, and Survey 3 which was conducted in 2003 (n=9081) when they were aged between 25 and 30 years.

The response rate for Survey 2 was 68% of women who had completed Survey 1. The response rate for Survey 3 was 64% of women who had completed Survey 1. Responses to a set of questions asking about the amount of stress felt in various areas of life were summarised to produce a mean stress score. The 10-item Center for Epidemiologic Studies Depression scale (CESD-10) was used to measure depressive symptoms. A multivariate logistic regression model, including the use of oral contraception and all covariates, was generated to predict the experience of depressive symptoms on Survey 3.

Oral contraception was used by 5342 (61.0%) women on Survey 2 and by 4202 (56.1%) women on Survey 3. There were 2488 (28.8%) women who reported depressive symptoms on Survey 2 and 1943 (25.9%) on Survey 3.

After adjusting for potential confounders, the odds of a non-user experiencing depressive symptoms is not significantly different from that of an oral contraceptive user (OR 1.05; 95% CI 0.09–1.21). Women who used oral contraceptives for reasons other than contraception were 1.32 (95% CI 1.07–1.62) times more likely to be depressed than women who used oral contraceptives for contraception. The percentage of women who reported experiencing depressive symptoms declined as the number of years of use increased (p=0.009). This effect plateaued after 5 years suggesting that survivor bias, whereby women who experience deterioration in mood or depressive symptoms which they associate with oral contraceptive use, were more likely to have stopped taking oral contraceptives prior to these surveys.

The authors conclude that the results suggest that after adjusting for confounders, there is no independent effect of oral contraceptive use on depressive symptoms in young Australian women.

O'Connell et al 2007 — Oral contraceptives: side effects and depression in adolescent girls [50]

This study investigated the side effects, including depression, of oral contraceptives in adolescent girls. A double-blinded randomised trial of oral contraceptives for dysmenorrhoea was conducted to assess side effects and depression. 76 adolescents received an oral contraceptive (ethinylestradiol 20 mcg + levonorgestrel 100 mcg) or a placebo for 3 months. Side effects were ascertained using open-ended and closed question formats. Participants self-administered the Center for Epidemiologic Studies Depression Scale (CES-D) to assess depressive symptoms.

57 participants (77%) reported at least one side effect. The number and type of side effects reported in the oral contraceptive group and in the placebo group were similar. Mean exit CES-D scores were comparable between groups.

The authors conclude that adolescents treated with an oral contraceptive or a placebo experienced similar numbers and types of side effects as well as depressive symptoms.

Svendal et al 2012 — The use of hormonal contraceptive agents and mood disorders in women [68]

The aim of this study was to investigate the association between current contraception use and mood disorders in a random, cross-sectional, population-based sample of women.

This study examined epidemiological data obtained from 498 women aged 20 to 50 years participating in the Geelong Osteoporosis Study (GOS). Mood disorders including major depressive disorder, minor depression, bipolar disorder, dysthymia, mood disorder due to a general medical condition and substance induced mood disorder were identified using a clinical interview (SCID-I/NP). Information on medication use and other lifestyle factors (past/current smoker, physical activity level, socioeconomic status, weight, medical conditions) were documented.

Those with a current mood disorder were more inactive, had a significantly higher number of medical conditions during the past year, were using more medicines, were more likely to have had past depression and were more likely to be using an antidepressant than those without a current mood disorder. There were no significant differences between the groups in terms of age, weight, SES and smoking status. Of the whole sample, 185 (37%) were using a contraceptive agent at the time of assessment. Of these, 152 (82%) were using combined hormonal contraceptives (oral and vaginal ring), while 33 (18%) were using progestogen-only contraceptives (oral, injectable, implant, IUD).

After adjusting for age and socioeconomic status (SES), women taking progestogen-only contraceptive agents had an increased likelihood of a current mood disorder (OR 3.0, 95% CI 1.1–7.8, p = 0.03) compared to those not taking progestogen-only contraceptive agents. In contrast, women currently taking combined contraceptive agents had a decreased likelihood of a current mood disorder (OR 0.3, 95% CI 0.1–0.8, p =

0.015) compared to those not taking combined contraceptive agents. These findings were not explained by weight, physical activity level, past depression, number of medical conditions or cigarette smoking.

The authors conclude that these data suggest a protective effect of the combined contraceptive pill and a deleterious effect of progestogen-only agents in regards to mood disorders.

Comments:

The confidence interval for the increased likelihood of a current mood disorder in women taking progestogen-only contraceptives compared to non-users is wide (OR 3.0, 95% CI 1.1–7.8). The sample size was likely too small to produce a more accurate finding.

Cinar et al 2012 — Effect of an oral contraceptive on emotional distress, anxiety and depression of women with polycystic ovary syndrome: A prospective study [36]

The authors aimed to determine the impact of oral contraceptive treatment on health-related quality of life (HRQOL), depressive and anxiety symptoms in polycystic ovary syndrome (PCOS). Limited data are available regarding the effects of an oral contraceptive on HRQOL and depressive and anxiety symptoms in PCOS. This study reports the effects of the ethinylestradiol+drospirenone (EE/DRSP) oral contraceptive on an HRQOL questionnaire for women with PCOS, depressive and anxiety symptoms after 6 months of treatment.

This prospective observational study included 36 patients presenting to an outpatient clinic in Turkey with PCOS between 1 June and 31 December 2007 without a previous psychiatric diagnosis. All participants completed the HRQOL questionnaire, Beck Depression Inventory (BDI), Hospital Anxiety and Depression Scale (HADS) and General Health Questionnaire (GHQ). Serum androgens, fasting insulin, fasting and postload glucose values during an oral glucose tolerance test were measured. Changes in these variables and the scores of questionnaires were evaluated after 6 months of treatment with EE/DRSP (30 mcg/3 mg).

The main complaints of the patients were hirsutism and irregular menses. After treatment, regular menstrual cycles were attained and hirsutism was significantly improved in all patients. Hirsutism and emotion domains of the HRQOL questionnaire improved at 6 months ($p < 0.05$ for both). BDI, HADS and GHQ scores did not show a significant improvement with oral contraceptive treatment. Overall, depression, anxiety mean scores and depression rates did not show a significant change. Among 8 depressive patients at baseline, 5 showed an improvement in BDI score at 6 months and 3 showed no significant change. In addition, 4 patients who were not depressed at baseline showed an increase in BDI score and were depressed after 6 months of treatment. The conversion rate of depression over the study period was 11.1% (4 of 36) and this change in depression rate after treatment was not significant.

The authors conclude that treatment with an oral contraceptive for 6 months in PCOS improves hirsutism and menstrual irregularities along with an improvement in quality of life. However, these benefits are not associated with amelioration of depression and anxiety in PCOS suggesting that oral contraceptives might have no influence on the natural course of psychiatric disorders in PCOS.

Comments:

This study had a small sample size (36 patients) and did not have information confounders such as diet and exercise. Depression was assessed based on screening tests and there was no clinical confirmation.

Tazegul Pekin et al 2014 — Depressive symptomatology and quality of life assessment among women using the levonorgestrel-releasing intrauterine system: an observational study [69]

The aim of this study was to examine the effect of the levonorgestrel-releasing intrauterine device (LNG-IUD) treatment on depressive symptoms, changes in bleeding patterns and quality of life among premenopausal women.

120 premenopausal women aged 18 to 50 years (median age 37 years, mean age 36.5 years) who sought care for menorrhagia from the Selcuk University Hospital in Turkey between September 2012 and

September 2013 were included. LNG-IUD was inserted into eligible patients after relevant evaluations. The pictorial blood assessment chart (PBAC) was used to evaluate participants' menstrual blood loss. All patients completed the 36-item Short-Form Health Survey (SF-36) for quality of life and a 13-term version of Beck's Depression Inventory for depressive symptoms. Both questionnaires were administered at the time of initial screening before and 6 months after insertion.

Results are summarised in Table 5. At the 6-month follow-up visit, the PBAC score considerably decreased ($p < 0.001$). For SF-36 scores, physical functioning, physical role limitations, emotional role limitations, bodily pain, vitality and mental health scores improved significantly after treatment ($p < 0.001$). Depression scores showed no significant difference from baseline to 6 months ($p = 0.375$).

The authors conclude that the LNG-IUD for treatment of menorrhagia increases quality of life but depression scores did not change significantly in 6 months.

Table 5: Description of dimensions of SF-36 and Beck depression levels before and after treatment

Parameters	Before treatment	After treatment	*p* value[a]	Change
PF	80 (55–90)	80 (65–90)	<0.001	0 (0–2.5)
RP	75 (25–100)	100 (50–100)	<0.001	0 (0–25)
BP	64 (51–84)	72 (61–85.5)	<0.001	9 (0–16)
GH	55 (40–72)	57 (42–72)	0.145	0 (−5 to 7)
VT	60 (45–80)	65 (55–75)	<0.001	0 (0–10)
SF	62.5 (50–87.5)	75 (62.5–87.5)	<0.001	0 (0–12.5)
RE	100 (33.3–100)	100 (66.7–100)	<0.001	0 (0–26.6)
MH	68 (52–80)	68 (60–80)	<0.001	0 (0–12)
PCS	64.2 (46.2–82.2)	76.0 (54.4–85.2)	<0.001	4 (0–12.8)
MCS	67.7 (48.0–82.1)	74.9 (56.2–84.4)	<0.001	4.1 (0–11.7)
Beck	8 (1–17)	7 (1–17)	0.375	0 (−3.5 to 3)

PF physical functioning, *RP* role limitations–physical, *BP* bodily pain, *GH* general health perceptions, *VT* vitality, *SF* social functioning, *RE* role limitations–emotional, *MH* mental health, *PCS* physical component summary score, *MCS* mental component summary score

[a] Wilcoxon Rank test

Toffol et al 2011 — Hormonal contraception and mental health: results of a population-based study [70]

The aim of this study was to analyse the association between the use of oral contraceptives and the levonorgestrel-releasing intrauterine device (LNG-IUD) on psychological well-being and psychopathology.

The associations between current use of oral contraceptives and the LNG-IUD, and their duration versus mood symptoms (Beck Depression Inventory; BDI), psychological well-being (General Health Questionnaire-12; GHQ-12) and recent psychiatric diagnoses (Composite International Diagnostic Interview; CIDI) were examined among women who participated in the Finnish population-based Health 2000 study. Analyses were performed on the 30 to 54 year old sample (n =2310; mean age 42.2 years) and some analyses were extended to include the younger age group (18 to 29 years; n = 913; mean age 23.4 years).

Of the 2310 women aged 30 to 54 years, 181 (9.5%, data missing for 410) were using oral contraceptives for contraception at the time of the interview. Results are summarised in Table 6. After controlling for the number of living children and for having given birth, no significant results were found between current oral contraceptive use and duration of use and GHQ total score in the 18 to 54 age group.

At the time of the interview, 212 women (11.2%, data missing for 410) aged 30 to 54 years were using the LNG-IUD for contraception. Significant negative correlations (controlling for age) were found between the current use of the LNG-IUD and the BDI total score. No significant correlation was found between current LNG-IUD use and GHQ total score or with any current psychiatric diagnosis. Overall, hormonal contraception was well tolerated with few significant effects on psychological well-being.

The authors conclude that the influence of hormonal contraception on mental health is modest and mainly favourable. The length of current oral contraceptive use seems to have some beneficial effects on mood although the longer the duration of use, the greater the association with a diagnosis of alcohol dependence. Knowledge of the use of hormonal contraception might be of value when assessing psychopathology in women. The cross-sectional design with partly retrospective data collection precludes any causal conclusions.

Table 6: Associations between BDI scores, GHQ scores and CIDI data versus current use of OCs and duration

	Current use			Duration of current use		
	n	B	95% CI	*n*	B	95% CI
BDI total score[a]	1675	−0.268	−1.279 to 0.742	164	−0.158	−0.334 to 0.018
GHQ-12 total score[b]	2502	0.088	−0.203 to 0.378	455	0.017	−0.042 to 0.076
CIDI[c]	*n*	OR	95% CI	*n*	OR	95% CI
Any psychiatric diagnosis	1685	1.460	0.958–2.224	164	0.983	0.907–1.066
Alcohol abuse	1718	0.000	—	164	—	—
Alcohol dependence	1715	1.922	1.000–3.692	164	1.485	1.134–1.944*
Major depressive episode	1723	1.221	0.688–2.168	163	0.928	0.831–1.037
Dysthymic disorder	1722	2.849	0.974–8.335	164	1.008	0.775–1.311
Major depressive disorder	1723	1.074	0.588–1.960	163	0.889	0.789–1.002
Anxiety disorder	1689	0.628	0.259–1.521	163	0.876	0.723–1.061

[a]Adjusted for age, professional status, marital status, educational level, bleeding pattern, current psychiatric diagnosis; sample: 30–54 years.
[b]Adjusted for age, professional status, marital status, educational level, lifetime psychiatric diagnosis; sample: 18–54 years.
[c]Adjusted for age, professional status, marital status, educational level, bleeding pattern; sample: 30–54 years.
*Significant at $P < 0.01$.

Toffol et al 2012 — Further evidence for lack of negative associations between hormonal contraception and mental health [7]

The authors' aim was to further study the association(s) between the use of oral contraceptives and the levonorgestrel-releasing intrauterine device (LNG-IUD) on psychopathology.

Data on adult women who participated in the national FINRISK Study Surveys in Finland in 1997, 2002 and 2007 were analysed. The survey was carried out through a self-administered questionnaire and a health examination. Presence of somatic and psychological symptoms was assessed by asking participants how often in the previous month they had had one or more out of 13 symptoms. Presence of depressed mood and anhedonia in the previous year was also assessed. Participants were also asked if they had been diagnosed or treated for depression or other psychological illness during the previous year. The presence and severity of depressive symptoms in the previous 2 weeks were assessed via a modified version of the 21-item Beck Depression Inventory (BDI) for 1997 and of the 13-item BDI for 2007. No BDI evaluation was available for 2002.

Overall, data for women aged 25 to 54 years (mean age 39.8 years) were available for 8586 women. A complete BDI-21 was available for 1505 women (54.3%) for 1997 and a complete BDI-13 was available for 1217 women (49.7%) for 2007. A diagnosis of depression in the previous year was reported by 456 women (7.9%) while 143 women (2.5%) reported having been diagnosed or treated for other psychological illness in the previous year.

At the time of the questionnaire, 1255 women (15.9%, data missing for 699) were using oral contraceptives for contraception. In logistic regression analyses, current use of oral contraceptives was not associated with any recent psychiatric diagnosis or with any recent symptom of depression or anhedonia. Conversely, duration of OC use was weakly positively associated with recent anhedonia. A negative association between the current use of oral contraceptives and Beck Depression Inventory-13 (BDI-13) score were found. Some other negative associations, all characterised by a small effect size were detected between current use of oral contraceptives and some BDI items.

At the time of the questionnaire, 759 women (9.7%, data missing for 791) reported using the LNG-IUD. In linear regression analysis (controlled for age, marital status, employment status, educational level, recent psychiatric diagnosis and having given birth), current use of the LNG-IUD was not associated with any recent symptom or with any BDI item or BDI total scores. In logistic regression analyses, neither current use of the LNG-IUD nor duration of use was associated with any recent psychiatric diagnosis or with any recent symptom of depression or anhedonia.

The authors conclude that the use of hormonal contraception is not associated with negative influence on mental health. Current oral contraceptive use seems to be associated with better mood, whereas the associations between duration of use of hormonal contraception and mental health effects are not clear.

Comments:

This study included many individual terms related to mental state. Some non-specific terms such as wet palms, sadness, crying, indecisiveness and exhaustion could be associated with day-to-day life or other health conditions.

Skovlund et al 2016 — Association of hormonal contraception with depression [71]

The authors investigated whether the use of hormonal contraception is positively associated with subsequent use of antidepressants and a diagnosis of depression at a psychiatric hospital.

This nationwide prospective cohort study combined data from the National Prescription Register and the Psychiatric Central Research Register in Denmark. All women and adolescents aged 15 to 34 years who were living in Denmark were followed up from 1 January 2000 to December 2013 if they had no prior depression diagnosis, redeemed prescription for antidepressants, other major psychiatric diagnosis, cancer, venous thrombosis or infertility treatment. Data were collected from 1 January 1995 to 31 December 2013. Use of different types of hormonal contraception was included. With time-varying covariates, adjusted incidence rate ratios (RRs) were calculated for first use of an antidepressant and first diagnosis of depression at a psychiatric hospital.

A total of 1,061,007 women (mean age 24.4 years, mean follow-up 6.4 years) were included in the analysis. Results are shown in Table 7. Compared with non-users, users of combined oral contraceptives had an RR of first use of an antidepressant of 1.2 (95% CI 1.22–1.25). Users of progestogen-only pills had an RR for first use of an antidepressant of 1.3 (95% CI 1.27–1.40). Higher risks were seen among women using the transdermal patch and vaginal ring compared with the corresponding pill but could be due to dose rather than route of administration.

Age-stratified analyses demonstrated decreasing RRs of a first use of antidepressants with increasing age for the most commonly used products. Analyses restricted to adolescents (aged 15 to 19 years) showed notably higher RRs of first use of antidepressants and first diagnosis of depression. Compared with non-users, users of combined oral contraceptives experienced a 1.8-fold higher rate (95% CI 1.75–1.84) of first use of antidepressants; users of progestogen-only pills experienced a 2.2-fold higher rate (95% CI 1.99–2.52). The RRs for a first diagnosis of depression at a psychiatric hospital were similar or slightly lower.

Assessment of association between the duration of use and the risk for first use of antidepressants demonstrated increasing relative risks with length of use. Relative risks peaked after 6 months of use. Thereafter relative risks decreased (Figure 1).

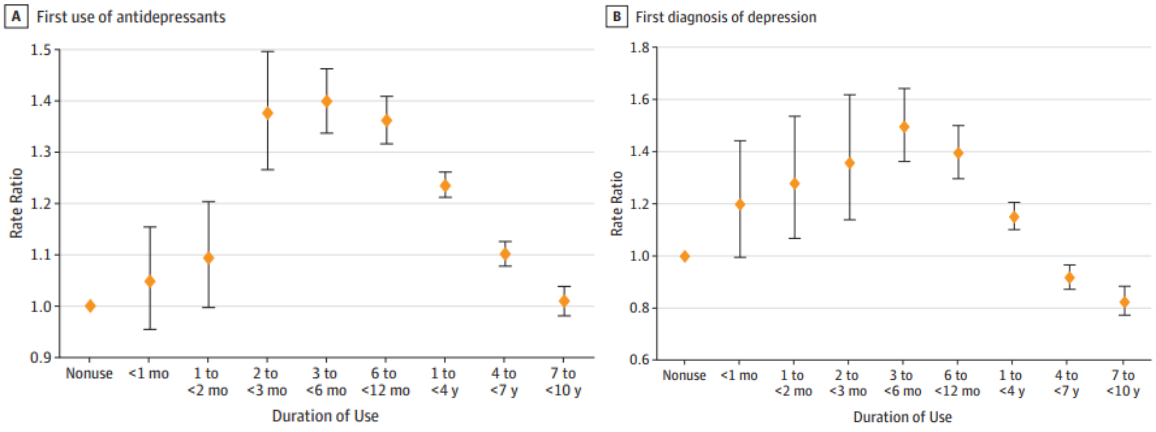

Figure 1: Rate ratios of first use of antidepressants and first diagnosis of depression

Rate ratios are stratified by length of hormonal contraceptive use. Participants with any use of hormonal contraception were excluded at first pregnancy. Error bars indicate 95% CIs.

Table 7: Rate ratio of first use of antidepressants and first diagnosis of depression in all women

Type of Hormonal Contraception	Person-years	First Use of Antidepressants			First Diagnosis of Depression		
		No. of Events	RR[b]	RR (95% CI)[c]	No. of Events	RR[b]	RR (95% CI)[c]
Nonuse	3 041 595	50 346	1	1 [Reference]	9310	1	1 [Reference]
All oral combined	3 518 381	74 126	1.2[d]	1.2 (1.22-1.25)[d]	12 211	1.0[d]	1.1 (1.08-1.14)[d]
All progestin-only	74 540	1884	1.3[d]	1.3 (1.27-1.40)[d]	296	1.1	1.2 (1.04-1.31)[d]
Combined products							
Oral							
Ethinyl estradiol, 50 µg							
Norethisterone	8060	176	1.5[d]	1.5 (1.26-1.69)[d]	22	1.3	1.2 (0.77-1.79)
Levonorgestrel	14 197	424	1.7[d]	1.6 (1.47-1.78)[d]	63	1.5[d]	1.4 (1.09-1.78)[d]
Ethinyl estradiol, 30-40 µg							
Norethisterone	38 927	583	1.0	1.1 (0.98-1.15)	77	0.9	0.9 (0.70-1.11)
Levonorgestrel	280 445	5618	1.2[d]	1.3 (1.22-1.29)[d]	1017	1.0	1.1 (1.02-1.17)[d]
Norgestimate	339 501	7017	1.1[d]	1.2 (1.18-1.24)[d]	1114	1.0	1.1 (1.00-1.14)[d]
Desogestrel	170 544	3918	1.3[d]	1.3 (1.27-1.35)[d]	604	1.1[d]	1.2 (1.07-1.27)[d]
Gestodene	757 337	15 759	1.2[d]	1.2 (1.18-1.23)[d]	2430	1.0	1.1 (1.03-1.13)[d]
Drospirenone	327 930	7843	1.3[d]	1.4 (1.34-1.41)[d]	1395	1.2[d]	1.3 (1.23-1.38)[d]
Cyproterone acetate	159 931	3914	1.3[d]	1.5 (1.43-1.52)[d]	638	1.2[d]	1.3 (1.17-1.38)[d]
Ethinyl estradiol, 20 µg							
Desogestrel	659 847	13 276	1.1[d]	1.2 (1.14-1.19)[d]	2199	1.0	1.1 (1.00-1.10)[d]
Gestodene	693 013	13 854	1.1[d]	1.2 (1.15-1.19)[d]	2314	1.0	1.1 (1.00-1.10)
Drospirenone	64 894	1623	1.2[d]	1.4 (1.31-1.44)[d]	309	1.2[d]	1.3 (1.15-1.44)[d]
Natural estrogen							
Dienogest	3711	119	1.7[d]	1.8 (1.49-2.14)[d]	29	1.8[d]	1.9 (1.31-2.72)[d]
Nonoral							
Patch (norgestrolmin)	8081	333	2.1[d]	2.0 (1.76-2.18)[d]	60	1.9[d]	1.7 (1.34-2.23)[d]
Vaginal ring (etonogestrel)	69 605	2195	1.5[d]	1.6 (1.55-1.69)[d]	421	1.5[d]	1.6 (1.45-1.77)[d]
Progestin-only products							
Oral							
Norethisterone	33 182	771	1.2[d]	1.3 (1.18-1.37)[d]	110	1.0	1.1 (0.88-1.29)
Levonorgestrel	1289	31	1.5[d]	1.7 (1.18-2.38)[d]	4	1.3	1.5 (0.54-3.86)
Desogestrel	40 069	1082	1.3[d]	1.4 (1.30-1.46)[d]	182	1.2[d]	1.2 (1.06-1.42)[d]
Nonoral							
Levonorgestrel IUS	81 281	2373	1.4[d]	1.4 (1.31-1.42)[d]	397	1.4[d]	1.4 (1.22-1.50)[d]

Abbreviations: IUS, intrauterine system; RR, incidence rate ratio.

[a] Includes 1 061 997 women aged 15 to 34 years.

[b] Adjusted for age and calendar year.

[c] Adjusted for age, calendar year, educational level, polycystic ovary syndrome, and endometrioses.

[d] Indicates statistical significance.

In this study, use of all types of hormonal contraceptives was positively associated with a subsequent use of antidepressants and a diagnosis of depression. This finding complies with the theory of progesterone involvement in the aetiology of depression because progestogen dominates combined and progestogen-only contraceptives. Adolescents seemed more vulnerable to this risk than women aged 20 to 34 years.

Comments:

This study used antidepressant use and diagnosis of depression at a psychiatric hospital as proxy measures for major, clinically relevant depression. Results on the occurrence or deterioration of major, clinically relevant depression are inconclusive. However, there is support for the occurrence of some mood effects in women using hormonal contraception.

Lundin et al 2017 — Combined oral contraceptive use is associated with both improvement and worsening of mood in the different phases of the treatment cycle—A double-blind, placebo-controlled randomized trial [72]

The authors aimed to prospectively estimate the severity of adverse mood in combined oral contraceptive users that would be as representative of general users as possible.

This multi-centre, randomised, double-blinded, placebo-controlled study included 202 healthy women. Women were randomised to a combined oral contraceptive (1.5 mg estradiol and 2.5 mg nomegestrol acetate) or placebo for three treatment cycles. Main outcome measure was the Daily Record of Severity of Problems (DRSP) which was filled out daily during one baseline cycle and the final treatment cycle.

Results from 84 women in the combined oral contraceptive group and 94 women in the placebo group were analysed. Combined oral contraceptive use was associated with small but statistically significant increases in mean anxiety (0.22; 95% CI 0.07–0.37, p = 0.003), irritability (0.23; 95% CI 0.07–0.38, p = 0.012), and mood swing scores (0.15; 95% CI 0.00–0.31, p = 0.047) during the intermenstrual phase but a significant premenstrual improvement in depression (-0.33; 95% CI -0.62 to -0.05, p = 0.049). Secondary analyses showed that women with previous adverse hormonal contraceptive experience reported significantly greater mood worsening in the intermenstrual phase in comparison with healthy women, $p < 0.05$. The proportion of women who reported a clinically relevant mood deterioration did not differ between those allocated to combined oral contraceptive (24.1%) or placebo (17%), p = 0.262.

The authors conclude that combined oral contraceptive use is associated with small but statistically significant mood side effects in the intermenstrual phase. These findings are driven by a subgroup of women who clearly suffer from combined oral contraceptive-related side effects. However, positive mood effects are noted in the premenstrual phase and the proportion of women with clinically relevant mood worsening did not differ between treatment groups.

Comments:

The combined oral contraceptive used in this study (1.5 mg estradiol and 2.5 mg nomegestrol) is known as Zoely in NZ. This particular contraceptive is approved but not currently available in NZ.

3.2 Company reports

3.2.1 Bayer (Annex 1)

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

3.2.2 Pfizer (Annex 2)

[redacted]

[redacted]

[redacted]

3.2.3 MSD (Annex 3)

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

3.3 CARM data

CARM identified 29 cases where a hormonal contraceptive was reported as the suspect medicine with any of the following: depression (with status=severe), anxiety (with status=severe) and suicidal ideation (including suicidal tendency, suicide attempt or suicide).

Of the 29 reports, 24 reported other reaction terms including emotional lability, psychosis aggravated, panic reaction, somnolence, personality disorder, irritability, mood swings, behaviour abnormal, aggressive reaction, anger, insomnia and fatigue. Age ranged from 18 to 47 years.

A summary of the reports is provided in Table 33. More detail on these reports is provided in Annex 4.

Table 33: Summary of cases reported to CARM

Contraceptive	Depression	Anxiety	Suicidal ideation	Combination of reaction terms	Total
Microgynon 30				1 x depression and anxiety	1
Norinyl-1	1				1
Diane-35				1 x depression and suicide attempt	1
Yaz		1	1	1 x depression and anxiety	3
Ginet				1 x anxiety, depression and suicidal tendency	1
Femulen	1				1
Cerazette	1	1			2
Jadelle	4	2		1 x depression aggravated and anxiety	7
Mirena	4			1 x depression and suicidal tendency 1 x depression and suicide attempt 2 x depression and anxiety	8
Depo-Provera	3			1 x depression aggravated and suicidal tendency	4
Total	**14**	**4**	**1**	**10**	**29**

4.0 DISCUSSION AND CONCLUSIONS

There are many different hormonal contraceptives approved and available for use. These are available in oral and non-oral forms and in various hormonal combinations. The many different types of hormonal contraceptives available and the inconsistent use of the terms depression and anxiety are both confounding factors in assessing their association. Suicidal ideation and its related terms are more easily defined but are much rarer and therefore more difficult to study. No studies could be identified that specifically assessed the risk of suicidal ideation with hormonal contraceptives.

The risk of depression with CHCs was first reported many years ago and the products and formulations available were quite different to those available now. It is not clear whether the products and formulations available now are more or less likely to be associated with depression compared to older products and formulations.

The life time prevalence of mood disorders is high particularly among females. Depressive disorders are part of a group of conditions and diseases dominated by a lowering of mood and often manifested with a variety of associated symptoms at psychological, behavioural and physiological levels. Mood disorders are characterised by a disturbance in the regulation of mood, behaviour and affect.

There are many factors that increase a person's vulnerability to depression. It is a complex condition influenced by both genetic and environmental factors. Monthly occurring depressive symptoms may be part of premenstrual tension syndrome (PMT) or the more severe variant known as premenstrual dysphoric disorder (PMDD). Some studies have found women with polycystic ovary syndrome (PCOS) are more likely to experience depressive symptoms than women without PCOS. These conditions add to the difficulty in distinguishing depression from other mood disorders and stress reactions.

Review of the published literature indicates that studies of hormonal contraceptives and the risks of severe depression, anxiety and suicidal ideation are heterogeneous. These studies often lacked appropriate validation of events, had small sample sizes and no differentiation between different types of hormonal contraception. These is a potential dual effect: alleviation of symptoms that occur with the menstrual cycle; and a small proportion of subjects possibly more likely to perceive symptoms as a mental disorder who report a negative effect on mood and mental wellbeing. In addition, reports of suicidal ideation are very rare making it difficult to draw any links between and increased risk with hormonal contraceptives compared to the background risk in those with mental disorders.

Postmarketing spontaneous reports of adverse reactions have well-known limitations. Reporting rates of adverse reactions obtained from these reports do not give an accurate measure of risk. Underreporting is an issue particularly for medicines that have been on the market for a longer period of time. Reporting rates are also influenced by other factors such as media attention and new scientific publications. In addition, it is even more difficult to compare risks of one hormonal contraceptive with another hormonal contraceptive as underreporting may differ between the two types of contraceptives.

Given the limitations in the available data, it is important that both healthcare professionals and consumers understand the size of these risks balanced with the well-known benefits of hormonal contraception in order to make an informed choice and to seek treatment or discontinue use if symptoms do occur.

5.0 ADVICE SOUGHT

The Committee is asked to advise:

- On the strength of the evidence for an association between hormonal contraceptives and severe depression, anxiety and suicidal ideation.
- Whether updates to data sheets are necessary.
- If this topic requires further communication other than MARC's Remarks in *Prescriber Update.*

6.0 ANNEXES

1. Bayer's review [confidential]
2. Pfizer's review [confidential]
3. MSD's review [confidential]
4. CARM data [confidential]

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