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REVIEW

Antipsychotic-induced hyperprolactinemia: synthesis of world-wide guidelines and integrated recommendations for assessment, management and future research

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Abstract
Rationale Hyperprolactinemia is a highly prevalent adverse effect of many antipsychotic agents, with potentially serious health consequences. Several guidelines have been developed for the management of this condition; yet, their concordance has not been evaluated.
Objectives The objectives of this paper were (1) to review current clinical guidelines; (2) to review key systematic evidence for management; and (3) based on our findings, to develop an integrated management recommendation specific to male and female patients who are otherwise clinically stabilised on antipsychotics.
Methods We performed searches of Medline and EMBASE, supplemented with guideline-specific database and general web searches, to identify clinical guidelines containing specific recommendations for antipsychotic-induced hyperprolactinemia, produced/updated 01/01/2010–15/09/2016. A separate systematic search was performed to identify emerging management approaches described in reviews and meta-analyses published ≥ 2010.
Results There is some consensus among guidelines relating to baseline PRL screening (8/12 guidelines), screening for differential diagnosis (7/12) and discontinuing/switching PRL-raising agent (7/12). Guidelines otherwise diverge substantially regarding most aspects of screening, monitoring and management (e.g. treatment with dopamine agonists). There is an omission of clear sex-specific recommendations. Systematic literature on management approaches is promising; more research is needed. An integrated management recommendation is presented to guide sex-specific clinical response to antipsychotic-induced hyperprolactinemia. Key aspects include asymptomatic hyperprolactinemia monitoring and fertility considerations with PRL normalisation.
Conclusion Further empirical work is key to shaping robust guidelines for antipsychotic-induced hyperprolactinemia. The integrated management recommendation can assist clinician and patient decision-making, with the goal of balancing effective psychiatric treatment while minimising PRL-related adverse health effects in male and female patients.

Keywords Hyperprolactinemia · Antipsychotic · Prolactin · Psychiatric treatment · Clinical guidelines

Background

Antipsychotic-induced hyperprolactinemia

Psychiatric disorders are debilitating conditions that also exert significant burden on patients' physical health (World Health Organisation 2001; Hert et al., 2011). Individuals with psychiatric disorders have an excess mortality two-three times higher than the general population (Hert et al., 2011). Antipsychotic drugs are the mainstay treatment for psychiatric disorders including schizophrenia, schizoaffective disorder and bipolar disorder, chronic conditions that require long-term or even lifelong treatment. Some antipsychotic-related physical adverse effects are well managed with structured protocols, for example clozapine monitoring (Bastiampillai et al., 2016) to prevent agranulocytosis, a deficiency in white blood cells. Yet, other physical adverse effects are less studied, underreported and not systematically assessed and managed (Hert et al., 2011).

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Hyperprolactinemia is defined as a condition of sustained prolactin (PRL) elevation. PRL is a 199-amino acid polypeptide hormone that is secreted by the lactotroph cells in the anterior pituitary under the inhibitory control of dopamine via D_2 receptors (Freeman et al., 2000). PRL levels vary within and across individuals and can be influenced by contextual factors (e.g. stress, exercise) (Bushe et al., 2010). Although there are discrepancies in both laboratory norms and the literature, a recent large epidemiological report considers normal levels to be < 28.3 ng/ml (< 600 mU/l) in women and < 16.5 ng/ml (< 350 mU/l) in men using a unit conversion calculation of 1 ng/ml = 21.2 mU/l (Soto-Pedre et al., 2016).

While psychiatric disorders by their very nature cause a range of receptor abnormalities, with internal regulatory processes plus stress having an effect on PRL secretion even in drug-naïve patients (Halbreich et al., 2003; Rybakowski et al., 2011), hyperprolactinemia is a highly prevalent, often untreated adverse effect of many antipsychotic agents. Antipsychotic agents block dopamine receptors in the tuberoinfundibular pathway of the hypothalamus. Dopamine release from the hypothalamus plays a pivotal role in the regulation of PRL secretion by inhibiting PRL synthesis and secretion. The dopamine blockade from antipsychotics therefore results in elevated PRL (Petty 1999, Halbreich et al., 2003; Bushe et al., 2010), with the extent of PRL elevation related to the affinity of the antipsychotic to D_2 receptors.

Antipsychotic-induced hyperprolactinaemia has been estimated to occur in up to 70% of patients with schizophrenia (Inder and Castle 2011). All first generation, typical antipsychotic agents are associated with significant hyperprolactinemia, while newer atypical agents are heterogeneous in their propensity for elevating PRL. Serum PRL levels 25–100 ng/ml (530–2120 mU/l) are typically associated with antipsychotic-induced hyperprolactinemia, although some agents can produce PRL levels in excess of 200 ng/ml (4240 mU/l) (Tewksbury and Olander 2016). Clinical symptoms result from the direct effect of PRL on target tissues, or indirectly via the hypothalamic-pituitary-gonadal axis (Grigg et al., 2016), and manifest differently in males and females. Female symptoms can include amenorrhea or menstrual irregularity and hirsutism, and male symptoms include gynaecomastia and oligospermia. Galactorrhoea, infertility, acne and sexual dysfunction can occur in both sexes (Milano et al., 2011). While PRL elevation is a prominent cause of sexual dysfunction (e.g. reduced libido and impotence in males), these symptoms can also be related to the disorder itself (i.e. due to negative symptoms, amotivation) or psychosocial factors (de Boer et al., 2015; Worsley et al., 2016). Hyperprolactinemia may result in multiple longer term health consequences including weight gain, reduced bone density/osteoporosis and fractures (Milano et al., 2011; Wang et al., 2014), though the relative contribution of antipsychotics currently remains unclear as persons with psychiatric disorders are at elevated risk for a number of lifestyle factors (e.g. smoking, reduced physical activity) also implicated in the onset of these adverse health effects (De Hert et al., 2016a, b). There is growing evidence for an increased risk of breast cancer (Wang et al., 2002; Milano et al., 2011), though again, data interpretation is complex due to the range of additional risk factors experienced by this patient population (De Hert et al., 2016a, b). There is preliminary evidence for increased risk of endometrial cancer, prostate cancer, pituitary tumours, immunosuppression, cardiovascular disease and depression (Milano et al., 2011; Montejo et al., 2016); however, further well-designed prospective research is required. Prolonged PRL elevation associated with long-term antipsychotic use may have further as yet unknown consequences.

Hyperprolactinaemia has been largely overlooked in clinical practice (Montejo et al., 2016). Clinical symptoms can go unnoticed by the patient or are perceived to be embarrassing (e.g. sexual dysfunction) and therefore not discussed. A recent study found that when prescribing PRL-raising antipsychotics, despite being aware of PRL-induced side effects, clinicians do not routinely screen their patients for elevated PRL or discuss potential consequences (Walsh and Lees 2012). The majority of clinicians are also not confident in the treatment of symptomatic hyperprolactinemia (Walsh and Lees 2012). This is concerning, since population-based data from patients with schizophrenia have shown PRL-related side effects to be significantly associated with medication nonadherence (DiBonaventura et al., 2012).

Current clinical guidelines for antipsychotic-induced hyperprolactinemia

The physical health consequences of hyperprolactinaemia due to prolonged antipsychotic use are significant, therefore warranting routine assessment and monitoring, and active risk reduction and treatment.

According to the definition proposed by the Institute of Medicine (1990), clinical practice guidelines are systematically developed statements that inform practitioner and patient decision-making. Guidelines aim to provide concise, consistent instructions to clinicians based on scientific evidence, to improve quality of care and minimise potential harms (Woolf et al., 1999). However, guidelines on the same clinical issue can vary in quality, and recommendations can be contradictory. This is a consequence of variable search methods and the allocation of different weightings on retrieved evidence and is more likely to occur when available evidence is less convincing (Barnes 2011).

The first known set of clinical recommendations specific to antipsychotic-induced hyperprolactinemia was produced in 2008 (Peveler et al., 2008). Recently, several new guidelines have emerged regarding the identification and management of antipsychotic-induced hyperprolactinemia. However, little is

known about the concordance between these guidelines, how recent key literature has been integrated into current recommendations, or how these guide sex-specific response to male and female psychiatric patients with chronic elevated PRL but who are clinically stabilised on antipsychotic medication.

Objective

The aim of this study was threefold: (1) to review current clinical guidelines for antipsychotic-induced hyperprolactinemia across three practice domains—screening, monitoring and management; (2) to review recent key literature pertaining to the management of patients with antipsychotic-induced hyperprolactinemia; and (3) based on our findings, to develop an integrated management recommendation for hyperprolactinemia, specific to male and female patients, who are otherwise clinically stabilised on antipsychotic medication.

Method

This study was conducted in three phases. Firstly, we used systematic methods to identify recent psychiatry, endocrinology and pharmacology guidelines and examined statements to provide a synthesis of current recommendations from these divergent fields regarding antipsychotic-induced hyperprolactinemia across screening, monitoring and management practice domains.

In the second phase, we identified and summarised key literature—recent systematic reviews and meta-analyses—reporting the efficacy and safety of emerging approaches to the management of antipsychotic-induced hyperprolactinemia.

The third phase involved integrating consensus with evidence, where available, into a management plan specific to male and female patients who are otherwise clinically stabilised on antipsychotic medication. Separate algorithms were developed for the management of male and female patients.

Guideline and key literature—inclusion criteria

Clinical guidelines

Guidelines were selected if they met the Institute of Medicine definition for clinical practice guidelines (Institute of Medicine 1990) and contained specific recommendations for the screening, monitoring and/or management of hyperprolactinemia resulting from antipsychotic use in adults ≥ 18 years. Selected guidelines were developed or endorsed by a professional organisation and produced or updated between January 1 2010 and September 15 2016. Selecting guidelines produced or updated from 2010 onward ensured currency of information in this review.

We excluded guidelines if they did not contain recommendations related to antipsychotic-induced hyperprolactinemia specifically, were not produced or endorsed by a professional organisation or were not relevant to at least one of our three practice domains of interest (i.e. screening, monitoring and/or management).

Recent key literature

Selected systematic reviews and meta-analyses were published between January 1 2010 and September 15 2016 and comprised data on the treatment of antipsychotic-induced hyperprolactinemia in patients aged ≥ 18 years. Reviews of paediatric and animal studies were excluded. Reviews of treatment for hyperprolactinemia due to other causes were also excluded.

Guideline and key literature—search methods

Clinical guidelines

Electronic searches of Medline and EMBASE were performed from inception to current date to identify all published clinical guidelines. Guidelines published prior to 2010 were excluded manually. Search strategies contained subject headings and key words for "hyperprolactinemia", "antipsychotic" and "guidelines" (see Appendices A and B). The reference lists of all relevant guidelines were then examined to identify further relevant guidelines. We also searched guideline-specific databases (e.g. Guidelines International Network, National Guideline Clearinghouse, National Institute for Health and Care Excellence) to identify relevant guidelines, supplemented with a general web search using the search terms: "(guideline*) AND (hyperprolactinemia OR hyperprolactinaemia) AND (antipsychotic*)".

Recent key literature

Then, we searched Medline, EMBASE and Cochrane Database for Systematic Reviews, supplemented with a general web search, to identify systematic reviews and meta-analyses published from 2010 onwards. This search strategy contained subject headings and key words for "hyperprolactinemia", "antipsychotic" and "systematic review" or "meta-analysis" (see Appendices C, D E).

Results

Clinical guidelines—screening, monitoring and management of antipsychotic-induced hyperprolactinemia

Our search of Medline and EMBASE for clinical guidelines retrieved 233 records, and the manual search retrieved 12 records, 36 of which were duplicates and were thus removed. Of the remaining 209 records, 194 were excluded based on inspection of the title/abstract. Fifteen full-text records were assessed for eligibility, with a further 3 records excluded (Fig. 1). Twelve records (Table 1) were identified to contain specific recommendations for the screening, monitoring and/or management of hyperprolactinemia resulting from antipsychotic use in adults age ≥ 18 years, per our inclusion criteria. Five of these records were specific guidelines on the management of antipsychotic-induced hyperprolactinemia (Kotecha 2013; Brown and Frighi 2015; NHS Foundation Trust 2015; Montejo et al., 2016; Tomova et al., 2016). Two of these records contained relevant recommendations from general hyperprolactinemia guidelines developed by Endocrinology Consensus Groups (Melmed et al., 2011; Rabinovich et al., 2013). Four of these records contained valid recommendations from clinical guidelines on the treatment and management of schizophrenia and related disorders (Barnes 2011; Hasan et al., 2013; National Institute for Clinical Excellence 2014; Galletly et al., 2016). One record contained valid recommendations from a set of psychiatry prescribing guidelines (Taylor et al., 2015). Guideline recommendations (and strength of evidence when this has been indicated by guideline authors) for each practice domain are described below, highlighting similarities and differences.

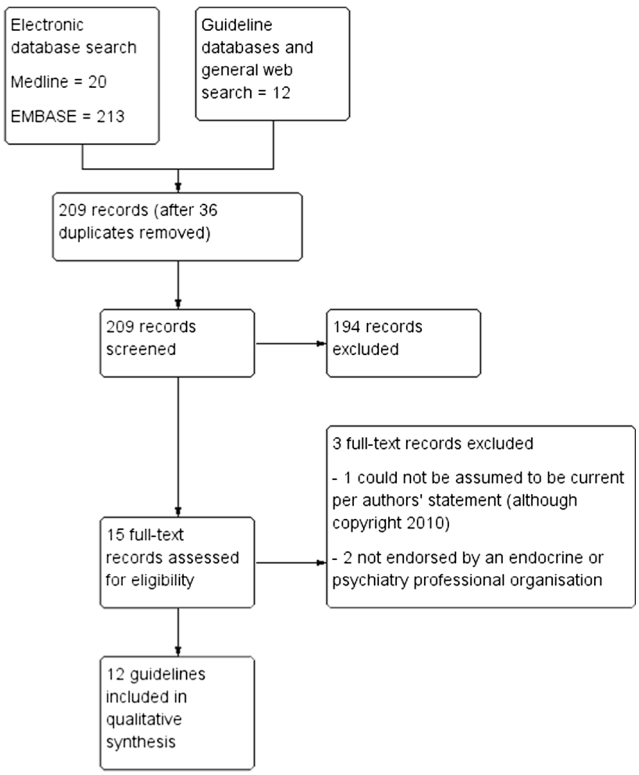

Fig. 1 Flow diagram of the search and inclusion of clinical guidelines for antipsychotic-induced hyperprolactinemia

Screening of antipsychotic-induced hyperprolactinemia

Screening PRL levels

Eight of the 12 included guidelines (Barnes 2011; National Institute for Clinical Excellence 2014; Brown and Frighi 2015; NHS Foundation Trust 2015; Taylor et al., 2015; Galletly et al., 2016; Montejo et al., 2016; Tomova et al., 2016) recommend baseline PRL levels to be measured prior to initiating antipsychotic medication. Two guidelines (Kotecha 2013; Tomova et al., 2016) provide specific recommendations for repeat sampling under ideal conditions (e.g. 1 h after waking, prior to taking medication, prior to eating) should an initial, random test show raised PRL. In contrast, three guidelines (Melmed et al., 2011; Rabinovich et al., 2013; Montejo et al., 2016) endorse only a single measurement of serum PRL to be sufficient when there has been no excessive stress from venepuncture. This recommendation, from the Endocrine Society, is reported to be based on high-quality evidence (Melmed et al., 2011).

Screening clinical symptoms

Three of the 12 included guidelines (Hasan et al., 2013; Kotecha 2013, Brown and Frighi 2015) recommend PRL levels to be measured only if hyperprolactinemia is suspected from clinical symptoms. Three guidelines (Kotecha 2013; Brown and Frighi 2015; Montejo et al., 2016) endorse taking a full sexual and menstrual history prior to initiating antipsychotic medication, so that a temporal relationship with any subsequent clinical symptoms can be established.

Screening for differential diagnoses

Seven guidelines (Melmed et al., 2011; Hasan et al., 2013; Kotecha 2013; Rabinovich et al., 2013; NHS Foundation Trust 2015; Galletly et al., 2016; Tomova et al., 2016) endorse eliminating the numerous pathological and physiological causes for hyperprolactinemia. These guidelines are not consistent in the conditions they recommend for exclusion. Four guidelines (Melmed et al., 2011; Rabinovich et al., 2013; Galletly et al., 2016; Tomova et al., 2016) specifically

Table 1 Summary of included clinical guidelines for antipsychotic-induced hyperprolactinemia

Guideline abbreviated name	Year produced/ updated	Author	Guideline	Guideline focus
BAP	2011	Barnes and the Schizophrenia Consensus Group of BAP	Evidence-based guidelines for the pharmacological treatment of schizophrenia: recommendations from the British Association for Psychopharmacology	Schizophrenia treatment
NICE	2014	Guideline Development Group (GDG)	National Collaborating Centre for Mental Health. Psychosis and schizophrenia in adults: Treatment and Management	Schizophrenia and psychosis treatment and management
RANZCP	2016	Galletly et al.	Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the management of schizophrenia and related disorders	Schizophrenia management
WFSBP	2013	Hasan et al. and WFSBP Task Force on Treatment Guidelines for Schizophrenia	World Federation of Societies of Biological Psychiatry Guidelines for Biological Treatment of Schizophrenia, Part 2: Update 2012 on the long-term treatment of schizophrenia and management of antipsychoticinduced side effects	Long-term schizophrenia treatment and management of side effects
Maudsley	2015	Taylor et al.	The Maudsley Prescribing Guidelines in Psychiatry, 12th Edition	Psychiatry prescribing
Endocrine Society	2011	Melmed et al. and Task Force of the Endocrine Society's Clinical Guidelines Subcommittee	Diagnosis and treatment of hyperprolactinemia: an Endocrine Society clinical practice guideline	Diagnosis and treatment of hyperprolactinemia
Spanish Guidelines	2013	Rabinovich et al. on behalf of the Neuroendocrinology Group of the SEEN	Clinical guidelines for diagnosis and treatment of prolactinoma and hyperprolactinemia	Diagnosis and treatment of prolactinoma and hyperprolactinemia
Spanish Consensus	2016	Montejo et al.	Spanish Consensus on the risks and detection of antipsychotic drug-related hyperprolactinaemia	Antipsychoticinduced hyperprolactinemia
NHS Foundation Trust: Northamptonshire Healthcare	2013	Kotecha	Guidelines for the management of antipsychotic-induced hyperprolactinaemia (MMG007)	Antipsychoticinduced hyperprolactinemia
NHS Foundation Trust: Sussex Partnership	2014	Tomova et al.	Guidance on the Treatment of Antipsychotic-induced Hyperprolactinaemia, Version 2	Antipsychoticinduced hyperprolactinemia
NHS Foundation Trust: Oxford Health	2015	Brown et al.	Antipsychotic-induced hyperprolactinaemia – Trust guideline for identification, monitoring and management	Antipsychoticinduced hyperprolactinemia
NHS Foundation Trust: Tees, Esk and Wear Valleys	2015	Drug & Therapeutics Committee	Hyperprolactinaemia: Guidelines for Patients and Clinicians (PHARM/0032/V5)	Antipsychoticinduced hyperprolactinemia

recommend pituitary imaging. Four guidelines (Melmed et al., 2011; Kotecha 2013; Rabinovich et al., 2013; Tomova et al., 2016) endorse assessment for macroprolactinemia—the larger, less biologically active PRL forms—when PRL levels are elevated typical symptoms are absent. One record (Rabinovich et al., 2013) provides guidance on differential diagnosis achieved through clinical history and physical examination. One guideline (Kotecha 2013) endorses consideration of potential causes not considered by other guidelines, specifically pregnancy, lactation and polycystic ovary syndrome. Ruling out pregnancy is reiterated in one other guideline (Rabinovich et al., 2013).

Trial 72-h cessation of antipsychotic

Four guidelines (Melmed et al., 2011; Rabinovich et al., 2013; NHS Foundation Trust 2015; Tomova et al., 2016) endorse a trial cessation of antipsychotic medication, for 72 h, followed by re-measurement of PRL level to ascertain drug effect when a baseline has not been established prior to initiating antipsychotic medication. The quality of evidence for this recommendation is reported in one guideline to be low, and the strength of the recommendation is indicated to be weak (Melmed et al., 2011). Only one guideline recommends substitution with an alternative, PRL-sparing antipsychotic if needed for the

management of psychotic symptoms during trial cessation (Melmed et al., 2011).

Monitoring of antipsychotic-induced hyperprolactinemia

Monitoring PRL levels

Guidelines diverge substantially regarding monitoring of antipsychotic-induced hyperprolactinemia. One guideline (Montejo et al., 2016) endorses routine, systematic PRL monitoring in *all* patients with ongoing antipsychotic treatment. Four guidelines (Barnes 2011; Brown and Frighi 2015; NHS Foundation Trust 2015; Montejo et al., 2016) recommend taking a serum measure 3 months after initiating the antipsychotic—one of which endorses repeat measures annually thereafter, suggesting a balance between what is ideal and what is appropriate (Barnes 2011). One guideline (Brown and Frighi 2015) endorses PRL level to be evaluated prior to 3 months if indicated by clinical symptoms. Two guidelines (Brown and Frighi 2015; Montejo et al., 2016) endorse PRL level be evaluated 3 months after any antipsychotic dose increase, or prior if clinically indicated. One guideline (Montejo et al., 2016) recommends frequency of PRL monitoring to be determined by degree of hyperprolactinemia. One guideline (Montejo et al., 2016) endorses monitoring of gonadal hormones along with PRL.

Monitoring clinical symptoms

A subset of guidelines emphasises monitoring of hyperprolactinemia via clinical symptomology. One guideline (Galletly et al., 2016) endorses 4–8- and 12-week evaluations when clinically indicated, and 24-week then annual evaluation for *all* patients. One guideline (Taylor et al., 2015) recommends symptom evaluation at 3, 6 and 12 months, obtaining a serum measure only if hyperprolactinemia is suspected. One guideline (Kotecha 2013) addresses patients' reluctance in reporting symptoms perceived to be embarrassing (e.g. sexual dysfunction, galactorrhoea) and recommends clinicians enquire specifically about these symptoms, facilitated by questionnaires if required. One guideline (Brown and Frighi 2015) provides a specific screening tool for antipsychotic-induced hyperprolactinemia, although frequency of clinical monitoring is not defined.

Secondary effect risk reduction

Emphasis on risk reduction of secondary effects varies substantially between the 12 included guidelines. Five guidelines (Hasan et al., 2013; Rabinovich et al., 2013; Taylor et al., 2015; Galletly et al., 2016; Montejo et al., 2016) endorse attention regarding the risk of osteoporosis with PRL-elevating antipsychotic use. Four of these guidelines (Rabinovich et al., 2013; Taylor et al., 2015; Galletly et al., 2016; Montejo et al., 2016) recommend bone mineral density testing when PRL is chronically elevated. One guideline endorses the evaluation of fracture risk in postmenopausal women, and in men over 50 years of age (Montejo et al., 2016). One guideline (Galletly et al., 2016) recommends breast screening and bone mineral density testing for female patients > 50 years, a recommendation that the guideline authors acknowledge to be currently associated with a lower level of evidence. One guideline (Montejo et al., 2016) endorses regular monitoring of breast and menstrual cycle changes in female patients of reproductive age and cautions amenorrhea persisting longer than 3 months, recommending intervention that restores menstruation due to risk of osteoporosis. The strength of this recommendation is reported by the authors of this guideline to be favourable (Montejo et al., 2016). One guideline (Brown and Frighi 2015) recommends addressing lifestyle factors that heighten risk for osteoporosis in patients with hyperprolactinemia, specifically smoking, sedentary lifestyle, vitamin D deficiency and alcohol intake. One guideline (Montejo et al., 2016) recommends taking a family history of osteoporosis, cancer and prolactinoma, which may increase risk of these secondary adverse effects.

Management of antipsychotic-induced hyperprolactinemia

Asymptomatic hyperprolactinemia

Six guidelines recommend against treating asymptomatic, antipsychotic-induced hyperprolactinemia (Melmed et al., 2011; Hasan et al., 2013; Rabinovich et al., 2013; Taylor et al., 2015; Galletly et al., 2016; Tomova et al., 2016). However, the authors of one of these guidelines report the quality of evidence for this recommendation to be low, and the strength of this recommendation to be weak (Melmed et al., 2011). Other guidelines depart from this recommendation—one guideline (Brown and Frighi 2015) endorses a dose reduction or switch if PRL levels are elevated. One guideline (Montejo et al., 2016) recommends clear cut-off points, recommending treatment of PRL levels > 50 ng/ml (> 1060 mU/l), and stipulating levels > 100 ng/ml (> 2120 mU/l) to always warrant intervention, even when no other symptoms are present. Two guidelines (Taylor et al., 2015; Tomova et al., 2016) recommend discussing the clinical implications of hyperprolactinemia with the asymptomatic patient.

Discontinuing, switching antipsychotics

Seven guidelines recommend discontinuing the PRL-raising agent (Melmed et al., 2011; Hasan et al., 2013; Rabinovich et al., 2013; NHS Foundation Trust 2015; Taylor et al., 2015;

Galletly et al., 2016; Tomova et al., 2016) and switching to a different antipsychotic as a first-line management approach for hyperprolactinemia. The Endocrine Society has graded the strength of this recommendation to be weak (Melmed et al., 2011). Two guidelines (Melmed et al., 2011; Tomova et al., 2016) recommend, when discontinuation is not feasible, to (1) reduce the dose of the PRL-raising agent, (2) switch to an alternative low potency or PRL-sparing agent or (3) add a full or partial dopamine agonist—with varying levels of caution provided. Three guidelines (Barnes 2011; Hasan et al., 2013; Brown and Frighi 2015) provide explicit caution regarding switching to an alternative, PRL-sparing antipsychotic. These three guidelines acknowledge that alternative antipsychotics still carry risk of significant predicted and unpredicted secondary effects, including risks of relapse and/or psychotic symptom exacerbation. Aripiprazole—as a substitute or in combination with the primary antipsychotic if aripiprazole monotherapy is not achievable—is recommended by four guidelines (Rabinovich et al., 2013; Brown and Frighi 2015; Taylor et al., 2015; Tomova et al., 2016). In the event that combination antipsychotic therapy is initiated, one guideline (Tomova et al., 2016) cautions that the primary antipsychotic's efficacy might be reduced due to partial agonism by aripiprazole at D_2 receptors, leading to competitive receptor occupancy. One guideline (Brown and Frighi 2015) recommends monitoring for increased risk of antipsychotic side effects.

Dopamine agonists

Guidelines diverge substantially about *when* to implement a dopamine agonist. All 12 guidelines caution this treatment approach citing potential exacerbation of psychosis, however with varying urgency. Three guidelines (Melmed et al., 2011; Rabinovich et al., 2013; Taylor et al., 2015) endorse treatment of symptomatic patients with a dopamine agonist, under strict control, when aripiprazole or other substitute is not tolerated as monotherapy, or in combination with the primary antipsychotic (Taylor et al., 2015). The quality of evidence for this recommendation is reported by the Endocrine Society to be low, and the strength of this recommendation to be weak (Melmed et al., 2011). One guideline (Brown and Frighi 2015) states that dopamine agonists should only be considered in *exceptional* circumstances. One guideline (Rabinovich et al., 2013) endorses dopamine agonists only when oestrogen/testosterone therapy is absolutely contraindicated. Other guidelines more readily endorse dopamine agonists for the treatment of antipsychotic-induced hyperprolactinemia. One guideline (Hasan et al., 2013) specifically recommends the addition of bromocriptine, although it is pointed out that RCTs to support this recommendation are lacking and that increased risk of psychotic relapse can be assumed. Another guideline (Tomova et al., 2016) recommends cabergoline as the first line preference when dopamine agonist therapy is used, and bromocriptine as second line (which the authors specifically caution as contraindicated in severe psychotic disorders). Amantadine is recommended to be used with caution, and quinagolide is suggested only as third line treatment for hyperprolactinemia. Dosing regimens for each dopamine agonist are provided in this guideline, while simultaneously pointing out that this treatment approach remains controversial and warrants specialist involvement (Tomova et al., 2016). One other guideline (NHS Foundation Trust 2015) suggests bromocriptine and cabergoline, but only when initiated by an endocrinologist.

Hormone treatments

Four guidelines (Melmed et al., 2011; Rabinovich et al., 2013; Galletly et al., 2016; Tomova et al., 2016) suggest a hormone strategy to treat hyperprolactinemia. Three of these guidelines (Melmed et al., 2011; Rabinovich et al., 2013; Tomova et al., 2016) endorse hormone treatment only when hypogonadism or low bone mass is evident and recommend hormone therapy (HT) or a combined oral contraceptive pill (OCP) for women, and exogenous testosterone for men, only with specialist advice. One guideline (Galletly et al., 2016) recommends adding oestrogen or testosterone to improve sexual dysfunction in female patients, citing evidence from randomised controlled trial data.

Alternative therapies

The herbal remedy, peony-glycyrrhiza decoction, is suggested by three guidelines (Hasan et al., 2013; Taylor et al., 2015; Tomova et al., 2016) for reducing hyperprolactinemia due to antipsychotic use. This treatment approach is cautioned in one guideline (Tomova et al., 2016) due to limited data and possible interaction with certain diseases or conditions.

Treatment algorithms

Three guidelines provide algorithms for the management of antipsychotic-induced hyperprolactinemia, differing in their approach based on the following: whether an antipsychotic has already been initiated (Brown and Frighi 2015), degree of baseline PRL elevation (NHS Foundation Trust 2015) and level of patient distress due to PRL-related symptoms (Kotecha 2013).

Screening, monitoring and management—special considerations

Patient involvement in decision-making

Three guidelines (Kotecha 2013; National Institute for Clinical Excellence 2014; Montejo et al., 2016) explicitly

Table 2 Summary of included systematic reviews

Author	Year	# of studies	Study type/s	Treatment	Primary outcomes
Hasani-Ranjbar et al.	2010	6	2 RCTs, 1 randomised cross-over trial, 2 open label trials with no control	1) shakuyaku-kanzo-to (TJ-68) 2) peony-glycyrrhiza decoction (PGD) 3) zhuangyang capsule 4) tongdatang serial recipe (TDT)	serum PRL, clinical improvement
Li et al.	2013	5	RCTs	adjunctive aripiprazole vs adjunctive placebo	adverse events + treatment efficacy as reported in trials
Meng et al.	2015	21	RCTs	adjunctive aripiprazole vs adjunctive placebo	proportion of patients whose PRL level returned to normal range
Bo et al.	2016	3	1 RCT, 2 cohort studies	adjunctive metformin	treatment efficacy (serum PRL, PRL related symptoms) + adverse drug reactions

recommend a collaborative approach to decision-making regarding antipsychotic use, including the provision of information to the patient and discussion of likely benefits and possible side effects. This recommendation is strongly graded in one set of guidelines (Montejo et al., 2016). One guideline (Montejo et al., 2016) explicitly considers the *impact* of side effects on the patient (e.g. sexual dysfunction, galactorrhea), recommending that this should guide treatment decision-making.

Women of childbearing age

Two guidelines (Barnes 2011; Taylor et al., 2015) caution women of childbearing age to be at particular risk of antipsychotic-induced hyperprolactinemia. One guideline (Taylor et al., 2015) recommends that long-term antipsychotic use be avoided in young women due to known (e.g. decreased bone mineral density) and possible (e.g. breast cancer) secondary risks.

Pregnancy planning

One guideline (Barnes 2011) provides clear recommendations for monitoring PRL levels should a woman be planning pregnancy. One guideline (Montejo et al., 2016) cautions use of PRL-raising agents in women planning pregnancy. Two guidelines (Rabinovich et al., 2013; Tomova et al., 2016) recommend any treatment with a dopamine agonist to be reviewed by an endocrinologist should pregnancy be planned and recommend discontinuation of bromocriptine to prevent foetal exposure (Rabinovich et al., 2013).

Preventing unplanned pregnancy

Four guidelines (Kotecha 2013; Brown and Frighi 2015; Galletly et al., 2016; Tomova et al., 2016) stipulate that, for women of reproductive age, switching to an antipsychotic with a lower propensity for PRL elevation—or when there has otherwise been successful management of hyperprolactinemia—compels patient education about normalisation of fertility and contraceptive use to prevent unplanned pregnancy. None of the guidelines caution the normalisation of fertility in male patients when PRL is normalised or significantly reduced.

Populations for use with caution

One guideline (Taylor et al., 2015) cautions PRL-raising agents in patients under 25 years, patients with osteoporosis and patients with a history of hormone-dependent breast cancer.

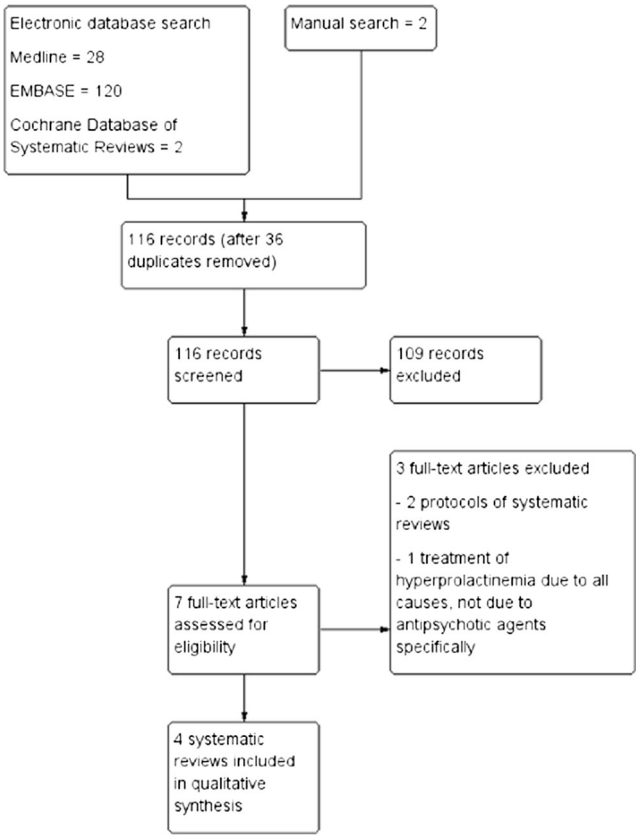

Fig. 2 Flow diagram of the search and inclusion of systematic reviews pertaining to the management of antipsychotic-induced hyperprolactinemia

Strength of evidence for recommendations

Two guidelines (Melmed et al., 2011; Rabinovich et al., 2013) provide graphical descriptions of recommendation strength and quality of evidence. Four guidelines (Barnes 2011; Hasan et al., 2013; Galletly et al., 2016; Montejo et al., 2016) provide grading of recommendations based on the level of evidence. Overall, even in guidelines using these systems, the majority of recommendations pertaining to antipsychotic-induced hyperprolactinemia are not graded. When grading is provided, strength of recommendations relating to antipsychotic-induced hyperprolactinemia is generally observed to be weak, based on low-quality evidence (e.g. uncontrolled studies).

Recent key literature—management of antipsychotic-induced hyperprolactinemia

From our second search, performed using Medline, EMBASE and Cochrane Database of Systematic Reviews, we identified 4 systematic reviews (2 of which contained meta-analysis) (Table 2) evaluating treatment approaches to antipsychotic-induced hyperprolactinemia. This electronic search retrieved 152 records, 36 of which were duplicates. A total of 109 records were excluded based on inspection of the title/abstract, and 7 records were assessed for eligibility with a further 3 records excluded (see Fig 2). A synthesis of the 4 systematic reviews matching our inclusion criteria is provided below.

Adjunctive aripiprazole

The first systematic review and meta-analysis of adjunctive aripiprazole for the treatment of antipsychotic-induced hyperprolactinemia was published in 2013 (Li et al., 2013). The authors identified five RCTs (total $N = 639$) for inclusion. Adjunctive aripiprazole was found to be superior to placebo in normalising PRL level: risk difference (Mantel-Haenszel, random) 0.76, 95% CI: 0.67 to 0.85, $p < 0.00001$. However,

General Principles of Good Practice

- When initiating an antipsychotic for your patient, obtain baseline PRL level (single measurement sufficient when there has been no excessive venepuncture stress)
- When initiating an antipsychotic, take a sexual history (and menstrual history for females), with which to compare any subsequent clinical symptoms
- Assess and document psychiatric illness response to the antipsychotic, to facilitate balanced decision-making based on antipsychotic effectiveness versus risks of prolonged elevated PRL (plus other potential adverse effects of the prescribed agent)
- Seek specialist involvement from an Endocrinologist, particularly when PRL levels are high (e.g. >100 ng/ml; >2120 mU/l), and when initiating hormone therapy for hyperprolactinemia
- PRL-raising agents are to be used with caution in patients under 25 years, women of child-bearing age, women planning pregnancy, patients with osteoporosis, patients with a history of hormone-dependent breast cancer
- In men, testosterone levels should be checked when hyperprolactinemia is identified. Maintaining testosterone levels within the normal range is important for bone health
- Take a collaborative approach to treatment decision-making, provide information to your patient, and discuss medication benefits and possible side effects, include shorter- and longer-term adverse effects relating to hyperprolactinemia. A risk reduction plan for the monitoring and management of antipsychotic side effects can be discussed with the patient
- The impact of secondary effects on the patient (e.g. reduced bone density) can assist in treatment decision-making
- Engage your patient in lifestyle changes to reduce risk of hyperprolactinemia-related adverse effects, e.g. smoking, sedentary lifestyle, vitamin D deficiency and alcohol intake contributing to osteoporosis

Fig. 3 General principles for risk reduction and management of hyperprolactinemia in patients stabilised on antipsychotic medication

the I^2 statistic = 43% indicated moderate-substantial heterogeneity. Lack of significant differences in discontinuation rates between adjunctive aripiprazole and placebo groups indicated treatment tolerability. Risk of bias due to allocation

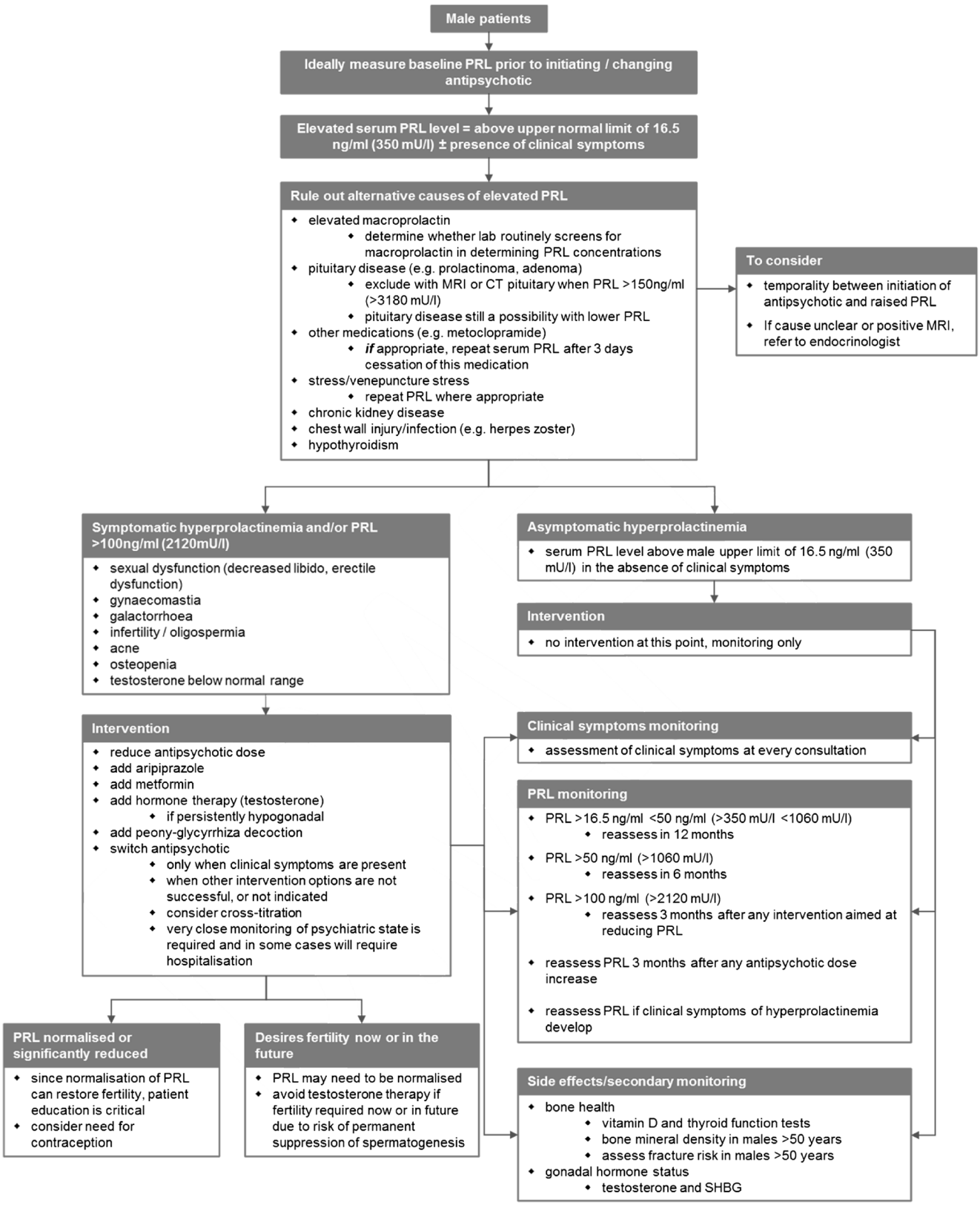

Fig. 4 Monash University Algorithm—management of hyperprolactinemia in male patients stabilised on antipsychotic medication

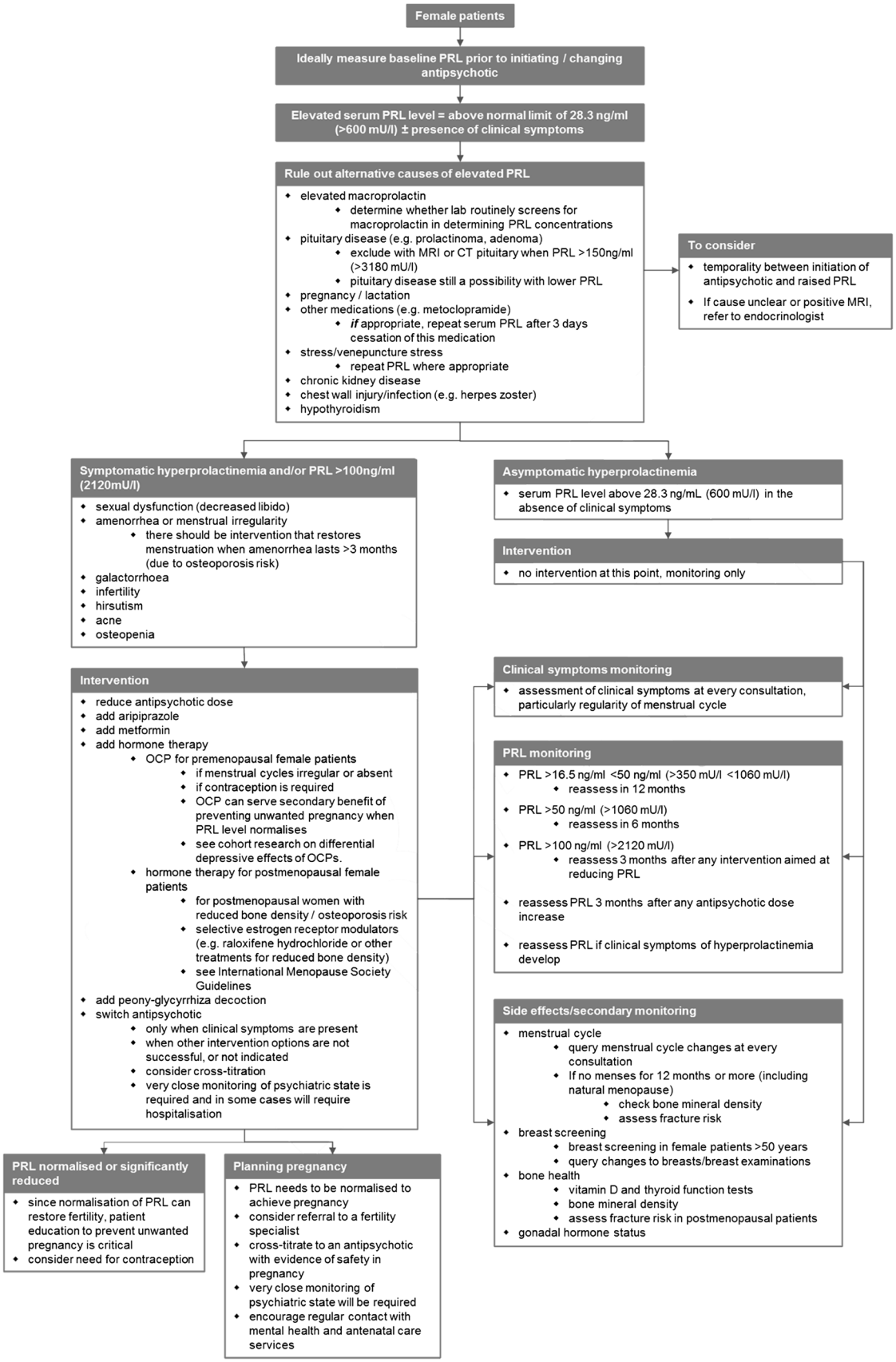

Fig. 5 Monash University Algorithm—management of hyperprolactinemia in female patients stabilised on antipsychotic medication

concealment was unclear across all five trials, and the randomisation method of one trial was identified to be at high risk of bias. Overall, included studies were found to vary from *low* to *high* in their quality of evidence (Li et al., 2013). However, despite these limitations and the small number of included trials, the authors concluded that adjunctive aripiprazole therapy is safe and effective in the management of antipsychotic-induced hyperprolactinemia, resulting in a 79% PRL normalisation rate within 1 week (Li et al., 2013; Peuskens et al., 2014).

A more recent systematic review comprising 21 studies examining adjunctive aripiprazole for antipsychotic-induced hyperprolactinemia, published in 2015 (Meng et al., 2015), revealed substantial concerns about the quality of data in RCTs being undertaken in this field of research. *All* 21 included studies were identified to be at medium to high risk of bias—insufficient methodological reporting was common across studies and, in particular, there was a frequent failure to report blinding and randomisation methods. Nearly half of the studies were graded *low* or *very low* in their quality of evidence. Publication bias was evident in that smaller studies reported greater treatment effects (Meng et al., 2015). A final meta-analysis of eight of these studies reporting the main outcome, recovery from hyperprolactinemia (total pooled $N = 604$), found aripiprazole to be an effective treatment for antipsychotic-induced hyperprolactinemia: RR = 19.17, 95% CI: 10.98 to 33.48. Meta-analysis showed tolerability of adjunctive aripiprazole: pooling the results of 12 studies containing comparable data (total pooled $N = 962$) found no statistically significant differences between adjunctive aripiprazole and placebo groups for proportion of participants to experience an adverse event. Short treatment duration was discussed as a serious limitation of the majority of included trials, given that treatment for antipsychotic-induced hyperprolactinemia in chronically unwell patients likely needs to be continuous. Based on their results, the authors of this review were more conservative in their recommendations than the preceding review stating that longer, more rigorous trials are required before aripiprazole can be endorsed as a treatment for antipsychotic-induced hyperprolactinemia (Meng et al., 2015).

Adjunctive metformin

The first systematic review of adjunctive metformin for the treatment of antipsychotic-induced hyperprolactinemia, published in 2016 (Bo et al., 2016), included one randomised controlled trial and two observational studies (total $N = 235$). Trial heterogeneity prevented meta-analysis being performed. Metformin was associated with a significant decrease in serum PRL levels across studies (mean = 54.6 μg/l) and was observed to be well-tolerated by patients. In the RCT, menstruation returned in 67% of patients with menstrual disturbances. This systematic review is limited in that it included observational studies that were graded to be at high risk of bias, and which were graded *very low* in their overall quality of evidence for primary outcomes (i.e. PRL level, PRL-related symptoms). Also, metformin dose-dependent effects on PRL levels were not evaluated. However, this review identifies metformin as a potential, emerging treatment for hyperprolactinemia resulting from antipsychotic use.

Herbal medicines

One systematic review, performed in 2010 (Hasani-Ranjbar et al., 2010), examined existing data on the efficacy of adjunctive herbal medications to manage drug-induced hyperprolactinemia. Six trials found four herbal supplements to be clinically effective and safe in the management of hyperprolactinemia due to antipsychotic use: shakuyaku-kanzo-to (TJ-68) (decreased serum PRL, clinical improvement), peony-glycyrrhiza decoction (PGD) (decreased serum PRL, clinical improvement), zhuangyang capsule (decreased serum PRL) and tongdatang serial recipe (TDT) (decreased serum PRL). However, the quality of included trials was low, and heterogeneity of the studies prevented a meta-analysis being performed. Still, when balancing potential efficacy and safety of herbal medicines with other agents used to treat hyperprolactinemia, the results of this review indicated that further research into the mechanisms of action and utility of these herbal preparations is warranted.

Two protocols for Cochrane systematic reviews have recently been published and plan to evaluate dopamine agonists (Gomes et al., 2012) and aripiprazole (Kolli et al., 2013) for hyperprolactinemia, the results of which are anticipated.

Discussion and integrated management recommendation

Synthesis of current clinical guidelines

In this review of current clinical recommendations, we identified that, while some concordance between guidelines is evident, there remains a lack of consensus regarding the screening, monitoring and management of hyperprolactinemia in adults who take antipsychotic medication. Overall, there was a strong reliance on clinical consensus within and across groups rather than scientific evidence. When grading was provided by guidelines, the strength of recommendations was generally observed to be weak, based on low-quality evidence. Further, recommendations were often not precise (e.g. clear cut-off PRL levels warranting intervention were only provided by one guideline (Montejo et al., 2016)). In particular, there was very little information available on sex-specific response to antipsychotic-induced PRL elevation; the

lack of recommendations explicit to men and women is a problematic omission.

The lack of clear and consistent recommendations observed may result from the propensity to nest recommendations for antipsychotic-induced hyperprolactinemia within broader clinical guidelines (e.g. schizophrenia management guidelines), without scope to provide clear details on all aspects of antipsychotic side-effect management. Other guidelines were identified through general web search and may be influenced by local peculiarities, or lack scientific rigour. However, this also reflects the shortage of studies that empirically examine factors that are critical to the formation of robust clinical guidelines (e.g. monitoring of asymptomatic hyperprolactinemia)—which tend to not be funding priorities. Indeed, the authors of one guideline (Buchanan et al., 2010) acknowledge that while hyperprolactinemia in patients taking antipsychotic medication warrants attention and treatment, there remains a lack of evidence to support strong recommendations. The reliance on consensus is a significant limitation of clinical guidelines for antipsychotic-induced hyperprolactinemia and likely reflects the lack of empirical data underpinning our management of this condition.

The majority of guidelines reviewed offered only non-specific recommendations for clinical care. For example, serum and clinical monitoring tended to be recommended, with only a minority of these guidelines specifying frequency and/or methodology. While the heterogeneity of patient populations and clinical settings limits the practicality of guidelines in providing fully articulate recommendations, more specific recommendations underpinned by empirical evidence would likely increase their utility (Institute of Medicine (U.S.) 2011), particularly when providing guidance on endocrinology abnormalities encountered in the psychiatric setting.

Four guidelines endorse a 72-h trial cessation of antipsychotic medication as an approach to establish true PRL levels. While this method of ascertaining drug effect on PRL levels may obliterate the need for pituitary imaging, these guidelines have not considered different PRL normalisation rates after discontinuation, which are not the same for all medications (Rabinovich et al., 2013). Risks of antipsychotic discontinuation (e.g. psychotic illness relapse or symptom exacerbation) also have not been routinely considered. Only one guideline (Melmed et al., 2011) graded this recommendation, reporting the quality of evidence underpinning the recommendation to be low.

Several guidelines recommend against treating asymptomatic hyperprolactinemia. However, one guideline (Melmed et al., 2011) graded this recommendation to be weak, due to the low quality evidence currently available. The incidence of asymptomatic hyperprolactinemia is estimated to be high at 32–49% (Johnsen et al., 2008; Park et al., 2016). This recommendation then challenges the utility of routine monitoring, in that monitoring would not extend to patients who are asymptomatic. Follow-up monitoring and subsequent management tended to be recommended only for symptomatic hyperprolactinemia, with the primary goal of treatment to restore gonadal and sexual dysfunction (which may then also prevent bone demineralisation) (Tomova et al., 2016). With emerging evidence of multiple severe health consequences of antipsychotic-induced hyperprolactinemia, and given that patients with psychiatric disorders are already at greater risk of osteoporosis, cardiovascular disease and other health conditions due to increased risk factors such as higher rates of smoking and alcohol use, research into the medium- and longer-term effects of antipsychotic-induced hyperprolactinemia is a clear priority and will serve to inform more robust clinical guidelines, especially for clinically silent, elevated PRL.

Switching antipsychotic agent was proposed as a primary management strategy for symptomatic hyperprolactinemia in the majority of guidelines. However, consideration of individual therapeutic and adverse response to a new, alternative antipsychotic agent was lacking overall. It is difficult to predict unique response to switching antipsychotics, which includes risk of new adverse effects and psychotic relapse. Effective switching is also challenged by variable pharmacokinetic and pharmacodynamic antipsychotic profiles, and the diversity of mechanisms underlying specific psychiatric disorders (Correll 2010). We observed that guidelines paid insufficient attention to these factors when switching was recommended. A further oversight of all guidelines recommending switching is that they did not consider the substantial proportion of patients who are resistant to multiple antipsychotic agents (Lieberman et al., 2005) for whom chronic antipsychotic use, and hyperprolactinemia, is more likely. Achieving optimal treatment of chronic psychiatric disorders requires careful therapeutic strategy to accomplish both efficacy and tolerability (Murru et al., 2016), and currently available empirical research into effective switching strategies needs to be better reflected in clinical guidelines aimed at improving tolerability issues.

Amantadine hydrochloride has been classified along with bromocriptine in one set of guidelines (Tomova et al., 2016) likely due to previous pre-clinical data showing this drug's direct and indirect effects on dopamine neurons. This non-competitive *N*-methyl-D-aspartic acid (NMDA) antagonist was associated with some positive effects in reversing antipsychotic-induced hyperprolactinemia in early open-label trials (Correa et al., 1987; Valevski et al., 1998); however, research interest has waned.

In relation to dopamine agonists, guidelines varied in their recommendations about when to implement these agents, which agent to use, and level of caution indicated due to potential exacerbation of psychotic symptoms. That endorsement of dopamine agonists is based on low quality of evidence, as reported in the Endocrine Society guidelines

(Melmed et al., 2011), is concerning. Given the risk of psychosis exacerbation, more research—including longer-term trials—is needed to determine the safety of dopamine agonists specific to psychiatric patients who take PRL-raising antipsychotic medications. We eagerly await the Cochrane systematic review of dopamine agonists for hyperprolactinemia, for which a protocol has recently been published (Gomes et al., 2012). Until then, that dopamine agonists are recommended by a number of guidelines, albeit cautiously, for treatment of hyperprolactinemia in psychotic patients is highly questionable.

In our review of current guidelines, we observed that there is limited guidance available regarding the management of milder versus more severe presentations of hyperprolactinemia. Risks associated with the *successful* treatment of hyperprolactinemia (i.e. thereby normalising PRL), such as restoration of fertility and unwanted pregnancy, have not been addressed by the majority of guidelines. Also, who bears the onus of overseeing the surveillance and management of hyperprolactinemia, and when specialist endocrine involvement is warranted, remains unclear (Jones 2014).

The PRL-raising effect of long-acting injectable (LAI) antipsychotics has attracted little clinical and empirical interest and has therefore been largely ignored within the guidelines. While LAIs have different adverse event profiles, some formulations (e.g. paliperidone, risperidone) are associated with greater PRL levels and PRL-related side effects, compared to oral antipsychotics (Gaebel et al., 2010; Franch et al., 2016; Gentile 2017). Cessation of oral antipsychotics typically results in PRL normalisation within 2–3 weeks; however, PRL can remain above pre-treatment values for 6 months or longer after discontinuation of some LAIs (Wistedt et al., 1981; La Torre and Falorni 2007). Still, LAIs can be highly advantageous in the chronic management of psychotic disorders and prevention of relapse due to poor treatment adherence (Miyamoto and Fleischhacker 2017). The integrated management recommendation presented in this review is also applicable to LAI-induced hyperprolactinemia. If PRL levels remain elevated after cessation of LAI, specialist referral to investigate this is warranted.

Our search extended to clinical guidelines in the management of bipolar disorder, another population for which there is widespread clinical use of antipsychotic medications. In three recent guidelines (Grunze et al., 2013; Yatham et al., 2013; National Institute for Health and Care Excellence 2014 (Updated 2016)), at best, hyperprolactinemia was discussed as a side effect of specific antipsychotics, with no information concerning screening, monitoring or management described, therefore not meeting our criteria for inclusion. Despite the likely health implications, it is clear that routine assessment and monitoring of antipsychotic treatment remains relatively neglected in bipolar disorder (Pacchiarotti et al., 2015).

A limitation of the current review is that we were not able to evaluate the *quality* of included guidelines, which meant that we were restricted to performing a narrative review incorporating systematic methods, rather than producing a systematic review of clinical guidelines per se. A strictly systematic approach would have utilised the Appraisal of Guidelines for Research and Evaluation-II (AGREE II) (Brouwers et al. 2010) instrument, which assesses methodological rigour and transparency of clinical practice guidelines; however, this instrument is not validated for assessing one component of a broader set of guidelines (i.e. rigour of screening for antipsychotic-induced hyperprolactinemia within guidelines for schizophrenia management).

Synthesis of key systematic literature—management of antipsychotic-induced hyperprolactinemia

In synthesising the findings of systematic reviews and meta-analyses pertaining to the treatment of antipsychotic-induced hyperprolactinemia, we agree with the authors of the more recent aripiprazole review (Meng et al., 2015) that the low quality, high risk of bias and short follow-up of many trials examining aripiprazole safety and efficacy to date raises concern about the validity of this treatment approach. Even though systematic review methods (Li et al., 2013; Meng et al., 2015) have not shown aripiprazole to be associated with a greater risk to safety, in general antipsychotic polytherapy has the potential to increase adverse effects and/or introduce new and unpredicted adverse effects. Also, adding aripiprazole has been hypothesised to lead to a reduction in the efficacy of the primary antipsychotic due to partial agonism by aripiprazole at D_2 receptors, leading to competitive receptor occupancy (Yokoi et al., 2002; Hoffer et al., 2009; Chen et al., 2010; Tomova et al., 2016). Given the potential serious risks of antipsychotic polytherapy, more rigorous trials of longer duration are clearly required before aripiprazole is indicated for antipsychotic-induced hyperprolactinemia. Current guidelines that recommend adjunctive aripiprazole for normalising PRL levels have not, for the most part, been transparent in the limitations of this treatment approach. Future updates of guidelines will need to consider findings of the recent, large systematic review (Meng et al., 2015) and also findings from an imminent Cochrane systematic review of aripiprazole for hyperprolactinemia, for which a protocol has recently been published (Kolli et al., 2013).

The 2010 systematic review of herbal medicines (Hasani-Ranjbar et al., 2010) similarly revealed the quality of included studies to be low. When balancing the potential utility and safety of herbal medicines with other agents used to treat hyperprolactinemia, more rigorous trials of herbal medicines and an updated systematic analysis are clearly warranted.

The 2016 systematic review of adjunctive metformin for antipsychotic-induced hyperprolactinemia comprised three studies that had all been published in the previous 3 years, indicating this agent to be an emerging, potentially clinically important treatment approach. Metformin is gaining increasing attention for its efficacy in reversing antipsychotic adverse effects including weight gain (Baptista et al., 2008; Ehret et al., 2010), insulin resistance (Ehret et al., 2010) and other metabolic abnormalities (Correll et al., 2013) and is also showing promise in lowering PRL levels. Additional RCTs are required to establish the utility of metformin in antipsychotic-induced hyperprolactinemia.

In general, further research into emerging treatments for antipsychotic-induced hyperprolactinemia is needed. Well-designed randomised controlled trials across all screening, monitoring and management domains, as well as systematic research of aggregate results, are required. For example, a systematic review of management approaches involving hormone modulation (e.g. oestrogen and testosterone supplementation) needs to be performed. Additionally, the timely transfer of research knowledge to routine clinical practice is required to improve response to antipsychotic-induced hyperprolactinemia.

The continued identification of safe, optimal adjunctive treatments for hyperprolactinemia will serve to increase antipsychotic treatment compliance, reduce nonadherence and offer long-term benefits in reducing risk associated with prolonged PRL elevation in psychiatric patients. This is particularly important when patients are otherwise clinically stabilised on an antipsychotic regime, for whom the mental health benefits of continuing on current medication may outweigh implementation of some strategies to reduce PRL levels recommended in clinical guidelines—still, hyperprolactinemia need not be an unavoidable side effect.

Integrated management recommendation

Based on our synthesis of recent clinical guidelines and key literature, the integrated management plan comprises a set of general principles for the management of hyperprolactinemia in patients stabilised on antipsychotic medication (Fig. 3), as well as algorithms to guide clinical response (Figs. 4 and 5). When one elevated PRL level is obtained (Soto-Pedre et al., 2016) in a patient who is stable on their antipsychotic medication (females > 28.3 ng/ml; > 600 mU/l, males > 16.5 ng/ml; > 350 mU/l) (Soto-Pedre et al., 2016), the algorithms provided, specific to male (Fig. 4) and female (Fig. 5) patients, can assist clinical decision making with the goal of balancing effective psychiatric treatment while minimising adverse consequences of hyperprolactinemia due to antipsychotic use.

In addition, based on our synthesis of recent clinical guidelines and key systematic literature, we outline the following specific points of consideration in the management of antipsychotic-induced hyperprolactinemia:

1. In asymptomatic cases, regular monitoring of serum PRL level should occur, with extent of PRL elevation driving the regularity of monitoring and also intervention response (Montejo et al., 2016). This is particularly important given emerging evidence of the multiple health consequences of chronic hyperprolactinemia.
2. Even when information on baseline PRL level is not available, we do not endorse trial cessation of antipsychotic medication to ascertain antipsychotic effect on true PRL level, given the risk of psychiatric symptom exacerbation and relapse, and based on the low quality, limited evidence available that currently supports this approach, as reported in the Endocrine Society guidelines (Melmed et al., 2011).
3. Intervention approaches for male and female patients outlined in the two algorithms presented (Figs. 4 and 5) are based on consensus between current guidelines, plus recent key systematic reviews and meta-analyses, and include antipsychotic dose reduction (Brown and Frighi 2015; Taylor et al., 2015; Tomova et al., 2016), the addition of aripiprazole (Rabinovich et al., 2013; Brown and Frighi 2015; Meng et al., 2015; Taylor et al., 2015; Tomova et al., 2016), metformin (Bo et al., 2016), hormone therapy (Melmed et al., 2011; Rabinovich et al., 2013; Galletly et al., 2016; Tomova et al., 2016) or peony-glycyrrhiza decoction (Hasan et al., 2013; Taylor et al., 2015; Tomova et al., 2016).
4. Switching antipsychotic to reduce PRL level should only be undertaken with extreme caution when the patient is mentally stabilised (Barnes 2011; Brockie and Brown 2015; Brown and Frighi 2015), only when clinical symptoms of hyperprolactinemia are present (Melmed et al., 2011; Rabinovich et al., 2013; Taylor et al., 2015; Galletly et al., 2016) and when other options for intervention are not successful, or not indicated.
5. Given the propensity of dopamine agonists to worsen psychotic symptoms, we do not endorse this approach for the treatment of hyperprolactinemia in patients with psychiatric disorders, at least until systematic analysis of available data (Gomes et al., 2012) can elucidate the balance of efficacy and risks in this patient population.
6. Premenopausal women with antipsychotic-induced hyperprolactinemia may benefit from intervention with the combined oral contraceptive pill (OCP), which can be used to resume menstruation. Recent nationwide cohort research has identified some hormonal contraception to be associated with onset of depression (Skovlund et al., 2016). When prescribing the OCP for hyperprolactinemia in psychiatric patients, it is pertinent to be aware of mood adverse effects. This report (Skovlund et al., 2016) can be

referred to for the specific rate ratios for depressive effects of different OCP preparations.

7. When considering hormone treatment for postmenopausal female patients with antipsychotic-induced hyperprolactinemia, refer to the International Menopause Society's (De Villiers et al., 2013) current recommendations for menopausal hormone therapy.
8. Selective oestrogen receptor modulators (SERMs) such as raloxifene hydrochloride are approved for use in the prevention and treatment of osteoporosis in postmenopausal women, and recent randomised clinical trials (Usall et al., 2015; Kulkarni et al., 2016) have shown adjunctive raloxifene to reduce psychotic illness severity in postmenopausal women with schizophrenia. However, safety and efficacy of raloxifene for osteoporosis due to *hyperprolactinemia* in this patient population remain to be evaluated in clinical trials (Grigg et al., 2016).
9. It is critical to educate female and male patients on the prevention of unwanted pregnancy when intervention goals are achieved (i.e. PRL normalises or is significantly reduced), which can restore fertility (Kotecha 2013; Brown and Frighi 2015; Galletly et al., 2016; Tomova et al., 2016).
10. When pregnancy is planned, PRL needs to be normalised and cross-titration to an antipsychotic with evidence of safety in pregnancy is recommended (Kulkarni et al., 2014). Antipsychotic agents are unavoidable to maintain the mental health and well-being of many women who have families. Very close monitoring of psychiatric state will be required, and regular contact with mental health and antenatal care services will optimise outcomes for both mother and infant. Clinicians and patients should be reassured that positive outcomes occur in the vast majority of pregnancies (Kulkarni et al., 2014).
11. A collaborative approach to treatment decision-making is recommended, which includes discussion of medication benefits versus potential short-term as well as longer-term side effects. A risk reduction plan for the monitoring and management of antipsychotic side effects can be discussed in collaboration with the patient.

Conclusion

Hyperprolactinemia need not be an unavoidable side effect of antipsychotic use. Clearer recommendations are required to assist clinician and patient decision-making regarding the oft-prolonged treatment of chronic psychiatric disorders, without which there will likely be greater clinical and ethical consequences from long-term use of PRL-raising agents (Montejo et al., 2016). This synthesis of current guidelines and integrated management plan, specific to male and female patients, is intended to inform assessment, management and future research regarding antipsychotic-induced PRL elevation.

Promising results from systematic reviews concerning emerging treatments, and increasing recognition of the physical health burden associated with this condition, should drive continued empirical research that shapes robust clinical guidelines. More empirical work is key to achieving our competing goals of improving and maintaining mental health, reducing adverse effects in order to improve treatment compliance and minimising the long-term health consequences of antipsychotic treatment for patients.

Compliance with ethical standards

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Appendix A
Database(s): Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

#	Searches	Results
1	Hyperprolactinemia/	2961
2	hyperprolactin?emia.ti,ab.	5732
3	exp Antipsychotic Agents/	113,542
4	antipsychotic*.ti,ab.	32,619
5	exp Practice Guideline/	21,920
6	exp Guideline/	28,500
7	exp Guideline Adherence/	25,525
8	guideline*.ti,ab.	246,580
9	(clinical adj3 (guideline* or guidance or standard? or protocol*)).ti,ab.	47,048
10	(national adj3 (guideline* or guidance or standard? or protocol*)).ti,ab.	16,508
11	(department* adj3 (guideline* or guidance or standard? or protocol*)).ti,ab.	1390
12	(practice adj3 (guideline* or guidance or standard? or protocol*)).ti,ab.	31,665
13	(society adj3 (guideline* or guidance or standard? or protocol*)).ti,ab.	3594
14	(institut* adj3 (guideline* or guidance or standard? or protocol*)).ti,ab.	7426
15	(board adj3 (guideline* or guidance or standard? or protocol*)).ti,ab.	714
16	(association adj3 (guideline* or guidance or standard? or protocol*)).ti,ab.	3919
17	1 or 2	6483
18	3 or 4	124,034
19	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16	313,469
20	17 and 18 and 19	20

Appendix B
Database(s): Embase 1974 to 2016 September 12

#	Searches	Results
1	Hyperprolactinemia/	9511
2	hyperprolactin?emia.ti,ab.	7334
3	exp Antipsychotic Agents/	247,714
4	antipsychotic*.ti,ab.	47,616
5	guideline*.ti,ab.	362,228
6	(clinical adj3 (guideline* or guidance or standard? or protocol*)).ti,ab.	65,937
7	(national adj3 (guideline* or guidance or standard? or protocol*)).ti,ab.	24,506
8	(department* adj3 (guideline* or guidance or standard? or protocol*)).ti,ab.	2387
9	(practice adj3 (guideline* or guidance or standard? or protocol*)).ti,ab.	42,927
10	(society adj3 (guideline* or guidance or standard? or protocol*)).ti,ab.	5760
11	(institut* adj3 (guideline* or guidance or standard? or protocol*)).ti,ab.	11,518
12	(board adj3 (guideline* or guidance or standard? or protocol*)).ti,ab.	982
13	(association adj3 (guideline* or guidance or standard? or protocol*)).ti,ab.	5405
14	exp practice guideline/	376,919
15	1 or 2	11,327
16	3 or 4	254,259
17	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14	657,971
18	15 and 16 and 17	213

Appendix C
Database(s): Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

#	Searches	Results
1	Hyperprolactinemia/	2978
2	hyperprolactin?emia.ti,ab.	5783
3	1 or 2	6536
4	Antipsychotic Agents/	48,899
5	antipsychotic*.ti,ab.	33,007
6	4 or 5	61,385
7	systematic review.ti,ab.	82,990
8	meta-analysis/	74,565
9	meta-analysis.ti,ab.	88,655
10	7 or 8 or 9	161,893
11	3 and 6 and 10	28

Appendix D
Database(s): Embase 1974 to 2016 October 19

#	Searches	Results
1	Hyperprolactinemia/	9849
2	hyperprolactin?emia.ti,ab.	7402
3	1 or 2	11,470
4	Antipsychotic Agents/	65,495
5	antipsychotic*.ti,ab.	47,989
6	4 or 5	90,337
7	systematic review.ti,ab.	100,240
8	meta-analysis/	150,109
9	meta-analysis.ti,ab.	111,353
10	7 or 8 or 9	221,508
11	3 and 6 and 10	120

Appendix E
Database(s): EBM Reviews - Cochrane Database of Systematic Reviews 2005 to October 19, 2016

#	Searches	Results
1	[Hyperprolactinemia/]	0
2	hyperprolactin?emia.ti,ab.	4
3	1 or 2	4
4	[Antipsychotic Agents/]	0
5	antipsychotic*.ti,ab.	182
6	4 or 5	182
7	3 and 6	2

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