Archives of Women's Mental Health (2019) 22:711–721
https://doi.org/10.1007/s00737-018-0933-z

REVIEW ARTICLE

Managing fibromyalgia syndrome in pregnancy no bridges between USA and EU

Salvatore Gentile[1] · Maria Luigia Fusco[2,3]

Received: 8 May 2018 / Accepted: 26 November 2018 / Published online: 3 January 2019

Abstract

The first aim of this article is to analyze the risk/benefit ratio of using psychotropic drugs approved in some countries for treating fibromyalgia syndrome (FMS) during pregnancy. Assessing the effectiveness of non-pharmacological interventions is the second scope of this article, in order to help clinicians to manage FMS in pregnancy in those countries were no drugs are approved for treating the disease. Following the PRISMA guidelines for systematic reviews, a literature search was conducted on PubMed and Google Scholar. Separate literature searches were performed for the three psychotropic drugs approved in the USA for treating FMS, psychotherapy, and transcranial magnetic stimulation (TMS). Perinatal duloxetine exposure is associated with increased risk of gestational and perinatal complications. With regards pregabalin, available information suggests that the drug is not devoid of structural teratogenicity potential. No data are available for milnacipran. Duloxetine and pregabalin should be only given to pregnant women diagnosed with severe forms of FMS after carefully weighing the benefits and risks for the mother-fetus dyad. On the other hand, we have to consider that the proportion of women who discontinue psychotropic drugs during pregnancy is as high as 85.4%. This figure raises further questions about adequate alternative treatment of FMS during the perinatal period. Moreover, neither duloxetine nor milnacipran or pregabalin have been approved by the EMEA for the treatment of FMS. Unfortunately, psychological treatment of FMS in perinatal women are not yet tested and data on TMS are conflicting.

Keywords Cognitive behavioral therapy · Duloxetine · Fibromyalgia · Milnacipran · Pregabalin · Transcranial magnetic stimulation

Introduction

In recent years, new research has added important insights to understanding of the landscape of perinatal psychiatry. New information is emerging about the nature of perinatal mood disorders and their impact on offspring. However, whereas a wide literature is available about the relationship between several maternal and psychiatric disorders and pre- and postnatal outcomes, such as anxiety and mood disorders, little is known about the course and the effects on fibromyalgia syndrome (FMS) on pregnancy.

Because the defining symptom of fibromyalgia is widely distributed pain, FMS is usually considered a pain disorder, at least in the rheumatology and pain communities. Nevertheless, in the updated 2010 fibromyalgia criteria of the American College of Rheumatology (ACR), only one of the five criteria items directly concerns musculoskeletal pain (Wolfe et al. 2011).

In other disciplines, such as psychiatry, psychology, psychosomatic medicine and, perhaps, general medicine, FMS is more often considered to be a symptom or psychosomatic disorder (Kroenke 2000). For this reasons, Wolfe et al. (2014) have suggested the inclusion of the syndrome among somatic symptom disorders (SSDs). It is also recommended that pregnant women with FMS should be screened for mood symptoms (Wolfe et al. 2014).

Recent reports suggest that the prevalence of FMS in pregnancy is rising in developed countries, such as the USA, actually interesting 0.06% of expectant mothers

✉ Salvatore Gentile
salvatore_gentile@alice.it

[1] ASL Salerno -Department of Mental Health, Mental Health Center Cava de' Tirreni Vietri sul Mare, Piazza Galdi, 1, 841013 Cava de' Tirreni, (Salerno), Italy

[2] Developmental Psychologist, Mental Health Institute, Torre Annunziata, (Naples), Italy

[3] Post-graduate School of Psychotherapy (SIPGI), Salerno, Italy

(Magtanong et al. 2017). Although recent reports suggest that FMS has no negative effect on pregnancy outcomes (Tulay et al. 2016), the study by Schaefer (2004) found that women with FMS had more symptoms of pain during pregnancy than healthy women. Moreover, severity of fibromyalgia symptoms may worsen during pregnancy (Schaefer 2004). In addition, pregnant women with FMS may experience significant pain, fatigue, and psychological stress, especially during the first 3 months (Schaefer 2004). Women with FMS are also more likely to use alcohol, tobacco, and illicit drugs. Such women are also at greater risk of developing gestational diabetes, preterm premature rupture of membranes, placental abruption, and births complicated by venous thromboembolism (Temple University 2006). The presence of fibromyalgia symptoms may impact on the course of delivery and the need for anesthesia (Saa'd et al. 2013). Of note, newborns of women with FMS are more likely to be premature and have intrauterine growth restriction (Magtanong et al. 2017; Zioni et al. 2011).

Areas covered

The first aim of this article is to analyze the risk/benefit ratio of using psychotropic drugs which have been approved in some countries for treating FMS.

In the USA, on June 13, 2008, the Food and Drug Administration (FDA) approved a new indication for duloxetine (DUL) HCl delayed-release capsules, allowing their use for the management of fibromyalgia in adults (Medscape 2008). DUL is a dual-action antidepressant and is a potent reuptake inhibitor of serotonin (5-HT) and norepinephrine (Trivedi et al. 2008). In the USA, DUL is also indicated for the treatment of major depressive disorder, diabetic neuropathic pain, stress urinary incontinence, and generalized anxiety disorder (Knadler et al. 2011). The drug achieves a maximum plasma concentration approximately 6 h after dosing. The elimination half-life of DUL is approximately 10–12 h. Only impaired hepatic function or severely impaired renal function warrant specific warnings or dose recommendations. However, the potential for pharmacokinetic interactions between DUL and drugs that inhibit CYP1A2 or drugs that are metabolized by CYP2D6 enzymes must be emphatized (Knadler et al. 2011).

On January 15, 2009, Forest Laboratories and Cypress Bioscience announced that the FDA approved milnacipran, a dual 5-HT- and norepinephrine reuptake inhibitor (SNRI), for the management of fibromyalgia. Whereas DUL has a 10-fold selectivity for 5-HT, milnacipran blocks 5-HT and norepinephrine reuptake with equal affinity (Stahl et al. 2005). The peak plasma concentration of unchanged milnacipran (~ 240 ng/ml) is attained at 3.5 h (Li et al. 2012). Evidence is accumulated suggesting that in animal models, milnacipran may exert pain-mitigating influences involving NE- and 5-HT-related processes at supraspinal, spinal, and peripheral levels of pain transmission (Leo and Brooks 2006).

In June 2007, pregabalin (PGB) became the first FDA-approved drug for specifically treating fibromyalgia. The drug is widely prescribed in neurology, psychiatry, and primary health care, and was granted marketing approval as an adjunctive therapy for partial-onset seizures, neuropathic pain, and, in some countries, including European countries, generalized anxiety disorders (Gentile 2014; Tassone et al. 2007). PGB is a gamma-aminobutyric acid which has shown high affinity for the α 2d calcium channel subunit expressed in the brain, spinal cord, skeletal and cardiac muscles (Weiss and Ivanova 2008).

Assessing the effectiveness of non-pharmacological interventions in treating FMS in pregnancy is the second scope of this article. This scope should help clinicians working in those countries were no drugs are approved to manage this clinical condition in this specific phase of the female reproductive cycle.

Methods

Following the PRISMA guidelines for systematic reviews (Liberati et al. 2009—see Fig. 1), an electronic literature search was conducted on PubMed (Medline) and Google scholar. The databases were searched from inception to the end of October 2018 by the two authors (S.G and M.L.F.) independently. Limits "*human*" and "*English language*" were applied. Abstracts and conference proceedings were excluded. Separate literature searches were performed for DUL, antidepressants, PGB, psycotherapy, fibromialgya, somatoform disorders, and transcranial magnetic stimulation (TMS). Eight search strings were created:

1. (("fibromyalgia"[MeSH Terms] OR "fibromyalgia"[All Fields]) AND ("pregnancy"[MeSH Terms] OR "pregnancy"[All Fields])) AND ("humans"[MeSH Terms] AND English[lang])
2. (("somatoform disorders"[MeSH Terms] OR ("somatoform"[All Fields] AND "disorders"[All Fields]) OR "somatoform disorders"[All Fields]) AND ("pregnancy"[MeSH Terms] OR "pregnancy"[All Fields])) AND ("humans"[MeSH Terms] AND English[lang])
3. ("antidepressive agents"[Pharmacological Action] OR "antidepressive agents"[MeSH Terms] OR ("antidepressive"[All Fields] AND "agents"[All Fields])

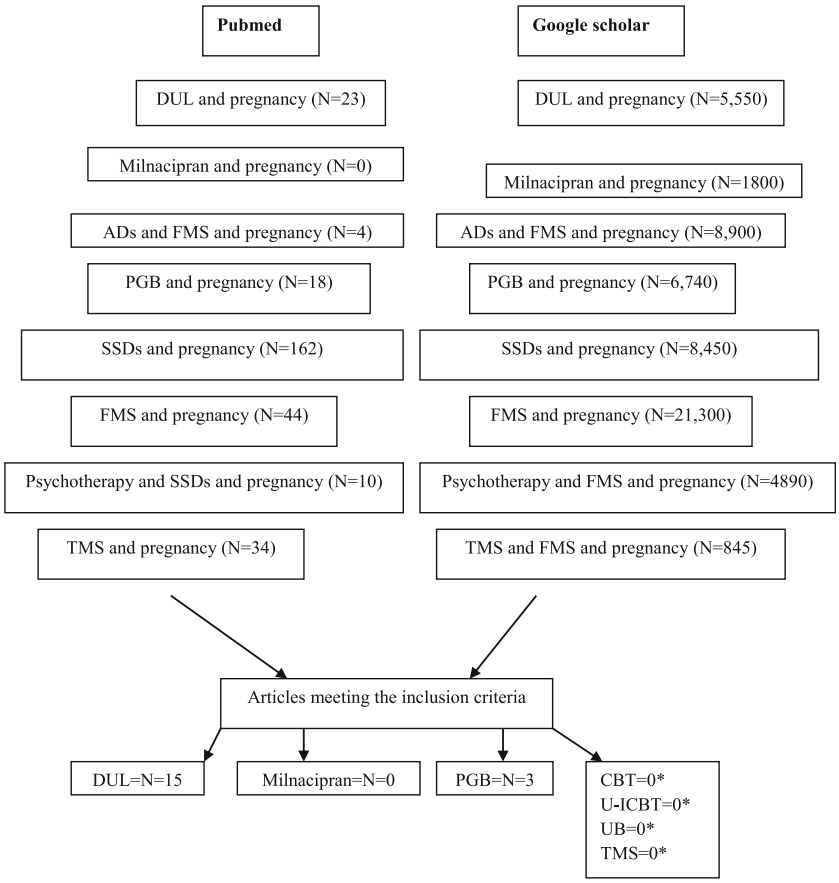

Fig. 1 Flow-chart of study selection process. Abbreviations: FMS, fibromyalgia syndrome; SSDs, somatoform disorders; CBT, cognitive behavioral therapy; U-ICBT, unguided internet cognitive behavioral therapy; UB, unguided bibliotherapy; TMS, transcranial magnetic stimulation. *Non-pharmacological interventions lacking of data about their own perinatal effectiveness (however, some of the most significant articles describing such interventions in FMS were also included in this review—see text)

OR "antidepressive agents"[All Fields] OR "antidepressants"[All Fields]) AND ("fibromyalgia"[MeSH Terms] OR "fibromyalgia"[All Fields]) AND ("pregnancy"[MeSH Terms] OR "pregnancy"[All Fields])) AND ("humans"[MeSH Terms] AND English[lang])

4. ("duloxetine hydrochloride"[MeSH Terms] OR ("duloxetine"[All Fields] AND "hydrochloride"[All Fields]) OR "duloxetine hydrochloride"[All Fields] OR "duloxetine"[All Fields]) AND ("pregnancy"[MeSH Terms] OR "pregnancy"[All Fields])) AND ("humans"[MeSH Terms] AND English[lang])
5. (milnacipram[All Fields] AND ("pregnancy"[MeSH Terms] OR "pregnancy"[All Fields])) AND ("humans"[MeSH Terms] AND English[lang])
6. (("pregabalin"[MeSH Terms] OR "pregabalin"[All Fields]) AND ("pregnancy"[MeSH Terms] OR "pregnancy"[All Fields])) AND ("humans"[MeSH Terms] AND English[lang])
7. ("psychotherapy"[MeSH Terms] OR "psychotherapy"[All Fields]) AND ("somatoform disorders"[MeSH Terms] OR ("somatoform"[All Fields] AND "disorders"[All Fields]) OR "somatoform disorders"[All Fields]) AND ("pregnancy"[MeSH Terms] OR "pregnancy"[All Fields])) AND ("humans"[MeSH Terms] AND English[lang])
8. ("transcranial magnetic stimulation"[MeSH Terms] OR ("transcranial"[All Fields] AND "magnetic"[All Fields] AND "stimulation"[All Fields]) OR "transcranial magnetic stimulation"[All Fields]) AND ("pregnancy"[MeSH Terms] OR "pregnancy"[All Fields]) AND ("humans"[MeSH Terms] AND English[lang])

All articles providing primary data on the use of DUL, milnacipram, and PGB in pregnancy were selected. For non-pharmacological interventions lacking of data about their own perinatal effectiveness, some of the most significant articles describing such interventions in FMS were also included in this review. The selected abstracts were analyzed separately by both authors (S. G. and M. L. F) to identify all relevant articles. The selected studies were discussed by the authors to select or exclude according to the eligibility criteria. There were no disagreements between the reviewers. Full texts were read if the information in the abstract was not sufficient to decide on inclusion or not.

Perinatal safety of duloxetine

Premise

Most of the studies on the perinatal safety of antidepressants were based on data extrapolated from single case reports or automated medical, administrative, and pharmacy insurance databases. Such database are unable to ascertain definitively that the women used or not the prescribed medication. Indeed, poor adherence to pharmacological treatments is a well-recognized problem in psychiatric practice, and this is especially true for patients specifically suffering from mood disorders (Gentile 2015).

Case reports

Five case report (see Table 1) are available on in utero exposure to DUL (Abdy and Gerhart 2013; Bellantuono et al. 2013; Boyce et al. 2011; Briggs et al. 2009; Eyal and Yaeger 2008). In all cases, no congenital malformations were recorded. However, as it happens with venlafaxine (Holland and Brown 2017), neonatal symptoms attributable to the onset of the Prenatal Antidepressant Exposure Syndrome (Gentile 2010) may also occur with DUL (Abdy and Gerhart 2013; Eyal and Yaeger 2008, see Table 1).

Analysis of pooled data from clinical trials/cohort studies

Hudson et al. (2005) integrated safety data were from the acute phases of eight double-blind, placebo-controlled trials in which patients were randomized to DUL for up to 9 weeks. Women who were pregnant or breastfeeding and women of childbearing potential not using medically accepted means of contraception were excluded from participating in such studies. Despite these precaution criteria, 28 pregnancies became exposed to DUL. No cases of fetal anomalies were reported.

Einarson et al. (2012) collected prospectively data on from either women or their health care providers who had requested information regarding the use of DUL during pregnancy. The study design included two comparison groups: the first included randomly selected women unexposed to DUL; in the second, women requiring information about exposure to non-teratogen agents were enrolled. No differences in the rate of major congenital malformations were recorded.

Similar results were reported by Källén et al. (2013) who analyzed data from the Swedish Medical Birth Register (1996–2011).

Hoog et al. (2013) reported cumulative information regarding outcomes of DUL-exposed pregnancies as captured, either retrospectively or retrospectively, in the Lilly Safety System (LSS) and the Food and Drug Administration Adverse Events Reporting System databases. The main study finding was that the frequency of abnormal outcomes reported in DUL-exposed pregnancies was consistent with the historic control rates in the general population.

In contrast, information retrospectively obtained from the Danish administrative health registries suggested an association between antenatal DUL exposure and increase in the risk of spontaneous abortion (Kjaersgaard et al. 2013).

Recently, a retrospective cohort study including Swedish offspring exposed to antidepressant medications and identified through maternal self-reported first-trimester antidepressant use and first-trimester antidepressant dispensations (Sujan et al. 2017) found a small increase in the risk of preterm birth. However, "although there were patients in this study who were exposed to DUL, the vast majority of the cases were exposed to SSRIs" (Sujan 2018).

DUL-induced pregnancy complications were also reported in a cohort study by Newport et al. (2016), who assessed information collected prospectively in a group of pregnant women participating in longitudinal observational studies in a tertiary referral center.

Such conclusions were confirmed by the Mother To Baby Pregnancy Study, which compared pregnant women who

Table 1 Case reports describing pregnancy outcomes following in utero exposure to duloxetine

Study	Maternal psychiatric diagnosis	Daily dose and timing of exposure	Concomitant psychotropic medications	Outcomes
Abdy and Gerhart (2013)	Bipolar disorder	90 mg before and throughout the pregnancy	Lamotrigine 100 mg daily; Quetiapine 800 mg daily	Hyperbilirubinemia, tremors, increased reflexes, hypertonia, tachypnea, irritability
Bellantuono et al. (2013)	Major depression	60 mg before and throughout the pregnancy	No	Healthy
Boyce et al. (2011)	Major depression	60 mg before and throughout the pregnancy	No	Healthy
Briggs et al. (2009)	Major depression	60 mg during the second half of pregnancy	No	Healthy
Eyal and Yaeger (2008)	Major depression, anorexia, and chronic neck pain	60 mg throughout the pregnancy	No	Respiratory distress, tremors, neonatal seizures

discontinued antidepressants at week 20 and women who continued antidepressant use ≥ 20 weeks of gestation for the risks of gestational hypertension and preeclampsia (De Ocampo et al. 2016).

More reassuring findings were conversely reported by Lupattelli et al. (2017) in The Norwegian Mother and Child Cohort Study, a prospective population-based study.

A recent study including 825 children exposed in utero to SNRIs excluded an association between antenatal antidepressant exposure and an increase in the risk of Autism Spectrum Disorders in children (Brown et al. 2017). Such studies have been summarized in Table 2.

Perinatal safety of milnacipran

Until now, no data have been published on pregnancy outcomes following gestational exposure to milnacipran. However, the Savella Pregnancy Registry is a US-based registry designed to monitor pregnancies exposed to milnacipran HCI. This is an observational, exposure-registration, and follow-up registry designed primarily to estimate the prevalence of major congenital anomalies, and secondarily to estimate the prevalence of recognized spontaneous abortions, stillbirths, induced abortions, minor congenital anomalies, and any serious adverse pregnancy outcomes among pregnancies exposed to Savella as well as adverse outcomes observed during the first year of life in offsprings born from these exposed pregnancies (The Savella Pregnancy Register 2009—last update: 2016). However, so far there is not an interim report available (Gioiella J, personal communication).

Perinatal safety of pregabalin

Studies on the reproductive safety of PGB (see Table 3) show several limitations, the main being the small number of PGB-exposed pregnancies with known outcomes, concomitant exposure to other medications, differences across groups in maternal conditions, and the high proportion of pregnant women treated for disorders in which PGB is not officially approved.

Registry-based studies

Patorno et al. (2017) performed a cohort study nested in the US Medicaid Analytic eXtract. The authors examined the risk of major congenital malformations among infants born to women exposed to PGB during the first trimester compared with women unexposed to anticonvulsants. The crude risk ratio of major congenital malformations for PGB was 1.80 (95% CI 1.26–2.58). However, this figure became non-statistically significant when calculated on women exposed to PGB-monotherapy (pooled RR 1.02; 95% CI 0.69–1.51). Such findings did not confirm the teratogenic effects of PGB, although the authors concluded that "they cannot rule out the possibility of a small effect."

A population-based study was performed to assess the comparative risk of spontaneous abortions, terminations of pregnancy, major birth defects, preterm births, and small for gestational age infants following intrauterine antiepileptic drug exposure in the Emilia Romagna, a Northern Italy region. Data were obtained from official health and administrative regional registries. Over a 3-year period, just 13 cases exposed to PGB during early pregnancy were identified (Mostacci et al. 2018).

Prospective studies

An observational prospective cohort study compared pregnancy outcomes in women exposed to PGB with those of matched controls. A significantly higher major birth defect rate in the PGB group was observed after exclusion of chromosomal aberration syndromes (Winterfeld et al. 2016).

Non-pharmacological treatments

Unfortunately, research on non-pharmacological interventions to treat antepartum mental disorder provides no information on SSDs.

In a recent meta-analysis assessing interventions to treat mental disorders during pregnancy, MedLine, PsycINFO, and Embase databases were searched by two independent reviewers for clinical trials with a control condition on treatment of women with antepartum mental disorders, including somatoform disorders. However, the authors identified just trials on patients with depressive or anxiety disorders. No trials on psychological treatment of SSDs in perinatal women were found (van Ravesteyn et al. 2017).

In non-pregnant women, there are various non-pharmacological approaches for treating SSDs (van Dessel et al. 2014). Hedman et al. (2016) investigated the effect of such treatments on SSDs. Using a randomized controlled design, 12 weeks of exposure-based CBT in the form of guided or unguided internet treatment or bibliotherapy led to large and significant improvements on the primary outcome compared with the control condition. Effects were maintained at long-term follow-up (6 months). Such results were confirmed by a recent meta-analysis which endorsed both efficacy and tolerability of CBT in reducing key symptoms and disability in FMS in the short- and long-term treatment if compared to waiting list, treatment as usual, attention controls, and active non-pharmacological therapies. Moreover, CBT did not differ in efficacy except superiority for coping with pain and tolerability from PGB and DUL (Bernardy et al. 2018).

Table 2 Analysis of pooled data from clinical trials and cohort studies pregnancy outcomes following in utero exposure to duloxetine

Study, *N*	Maternal psychiatric diagnosis	Daily dose and timing of exposure	Concomitant psychotropic medications	Outcomes
Hudson et al. (2005) *N* = 28	Major depressive disorder	40–120 mg first trimester	No	No cases of congenital anomalies
Einarson et al. (2012) *N* = 208	N/A	N/A Through early pregnancy in the 99% of the cases	N/A	No increase in the risk of congenital anomalies (3 cases of fetal anomalies reported (clubfoot, kidney agenesis, hydronephrosis)
Källen et al. (2012) *N* = 286	N/A	N/A 2nd and/or 3rd trimester	N/A	No increase in the risk of congenital anomalies (7 cases of fetal anomalies reported)
Hoog et al. (2013) *N* = 400 (LSS) *N* = N/A (AERS)	In most of cases (74%), depression or post-partum depression; in the other cases, anxiety, other psychiatric disorders, urinary incontinence, pain, neuropathy, or fibromyalgia	N/A	N/A	No increase in the risk of spontaneous abortions, premature births, post/perinatal complications
Kjaersgaard et al. (2013) *N* = N/A	Depression	N/A	No	Increased risk of spontaneous abortions (RR 2.12, 95% CI 1.52–2.96)
Sujan et al. (2017) *N* = N/A	N/A	N/A First trimester	No	Increased risk of preterm birth (OR 1.35; 95% CI 1.28–1.42) No increase in the risk of small for gestational age, ASDs, and ADHD
Newport et al. (2016) *N* = 14	In most of cases (84%), mood disorders	N/A After week 20 of gestation	No	Increased risk of hypertensive disorders (OR 2.12, 95% CI 1.52–2.96)
De Ocampo et al. (2016) *N* = 38 (including VEN-exposed)	N/A	N/A Participants who reported use of antidepressants were classified as discontinuers (women who discontinued use < 20 weeks of gestation) or continuers (women who continued use ≥ 20 weeks of gestation)	No	Increased risk of hypertensive disorders (OR 1.83; 95% CI 1.05–3.21)
Lupattelli et al. (2017) *N* = N/A	Depressive and anxiety symptoms	N/A Early and mid pregnancy	No	No increased risk of preeclampsia
Brown et al. (2017) *N* = N/A	Mood and anxiety disorders	N/A Pregnancies were considered exposed during a specific trimester if 1 or more prescriptions were filled during that trimester, or if the prescription duration overlapped with that trimester	N/A	No increased risk of ASDs

LSS Lilly Safety System, *AERS* FDA Adverse Events Reporting System, *RR* relative risk, *OR* odds ratio, *CI* confidence interval, *VEN* venlafaxine, *ASDs* Autism Spectrum Disorders, *ADHD* Attention-Deficit/Hyperactivity Disorder

Table 3 Registry-based and prospective studies describing pregnancy outcomes following in utero exposure to pregabalin

Study, *N*	Maternal psychiatric diagnosis	Daily dose and timing of exposure	Concomitant psychotropic medications	Outcomes
Mostacci et al. (2018) *N* = 30	N/A	N/A First trimester (*N* = 13)	N/A	1 case of major birth defect (cardiac malformation)
Patorno et al. (2017) *N* = 477	Pain (most often neuropathic pain, *n* = 151), psychiatric disorders (depression, anxiety disorder, bipolar disorder, *n* = 241), epilepsy (*n* = 32)	N/A First trimester	Yes	No increased risk of major birth defects (28 cases of fetal malformations) Pooled RR 1.02 95% CI 0.69–1.51
Winterfeld et al. (2016) *N* = 164	Pain (most often neuropathic pain, *n* = 115), psychiatric disorders (depression, anxiety disorder, bipolar disorder, psychosis, *n* = 39), epilepsy (*n* = 5), and restless legs syndrome (*n* = 1)	N/A First trimester	Yes	Increased risk of major birth defects (8 cases of structural anomalies, 4 involving the CNS, 2 the skeletal system, 2 the cardiac system, 1 the skin/vascular system OR 3.0 95% CI 1.2–7.9

OR odds ratio, *RR* risk ratio, *CI* confidence interval, *CNS* central nervous system

Among non-pharmacological interventions, recent preliminary findings seem also to suggest that innovative neuromodulating techniques, such as transcranial direct current stimulation, could have pain-relieving effects in the treatment of FMS. Such effects could be mediated by changes in serum beta-endorphin levels (Khedr et al. 2017). However, such conclusions require further confirmations. In fact, a recent meta-analysis showed a decrease in pain severity before and after stimulation below the clinically relevant threshold (1.5 points) (Saltychev and Laimi 2017). Moreover, available data do not support the effectiveness of whole body vibration exercise training in reducing key symptoms of FMS, such as pain intensity, stiffness, fatigue, and physical function (Bidonde et al. 2017). Peripherally acting agents, such as nutritional supplements, also demonstrated no evidence for efficacy in attenuating core-symptoms of FMS (Henningsen et al. 2018).

Discussion

A recent study has shown that serotonin levels in pregnant women with FMS are lower than the control group and that such levels reduce as pregnancy progresses. Anxiety and depression in pregnant women with FMS are higher than in the control group. The presence of depression increases the likelihood of developing FMS at a statistically significant level (Atasever et al. 2017). Thus, the rationale exists suggesting the use of DUL in pregnant women with FMS and, especially, for those forms rated by the DSM-V (APA 2013) as severe and complicated by depressive symptoms (see Table 4).

Obviously, women should be informed about the teratogenic risks associated with DUL. Recent findings suggest that the concept of teratogenicity is a complex phenomenon with different aspects: beyond the "historical" concept of *structural teratogenicity* (which identifies the risk of major fetal malformations), three others aspects must be considered: *perinatal teratogenicity* (a definition which stresses the risk of perinatal complications in newborns exposed to psychotropic drugs through placenta); *gestational teratogenicity* (this definition highlights the risk of complicated pregnancy outcomes related to psychotropic medication exposure in pregnancy); and *neurobehavioral teratogenicity* (which identifies the risk of impaired neurodevelopmental outcomes in children exposed in utero to psychotropics). Reviewed data suggest that main clinical concerns associated with perinatal DUL exposure are as follows:

a) gestational teratogenicity [increased risks of gestational hypertension; (De Ocampo et al. 2016; Newport et al. 2016)]. At the time of writing, data on the risk of other gestational complications are still conflicting (Hoog et al. 2013; Kjaersgaard et al. 2013; Sujan et al. 2017).
b) perinatal teratogenicity (Abdy and Gerhart 2013; Eyal and Yaeger 2008). Despite this risk is just suggested by two case reports, we have to remember that another dual-action antidepressant, venlafaxine (which shows more exhaustive reproductive safety data), has been definitively associated with an increase in the risk of PAES (Holland and Brown 2017). With regards specifically the risk of persistent pulmonary hypertension in the newborn, data are still uncertain (Bérard et al. 2017).

Moreover, in 2008, the European Medicine Agency (EMEA) did not approve the use of DUL in FMS. The main concerns raised by the European Committee for Medicinal Products for Human Use (CHMP) were that the short-term effect was not robustly demonstrated. Furthermore, the small

Table 4 Somatic symptom disorder (SSD). DSM-V diagnostic criteria and severity rating. Clinical management

DSM-V diagnostic criteria	DSM-V severity rating	Clinical management
A. One or more somatic symptoms that are distressing or result in significant disruption of daily life B. Excessive thoughts, feelings, or behaviors related to the somatic symptoms or associated health concerns as manifested by at least one of the following: *1.* Disproportionate and persistent thoughts about the seriousness of one's symptoms *2.* Persistently high level of anxiety about health or symptoms *3.* Excessive time and energy devoted to these symptoms or health concerns C. Although any one somatic symptom may not be continuously present, the state of being symptomatic is persistent (typically more than 6 months) *Specify* if: With predominant pain (previously pain disorder): This specifier is for individuals whose somatic symptoms predominantly involve pain *Specify* if: Persistent: A persistent course is characterized by severe symptoms, marked impairment, and long duration (more than 6 months)	Mild: Only one of the symptoms specified in Criterion B is fulfilled. Moderate: Two or more of the symptoms specified in Criterion B are fulfilled. Severe: Two or more of the symptoms specified in Criterion B are fulfilled, plus there are multiple somatic complaints (or one very severe somatic symptom)	USA In severely ill patients: Duloxetin *Concerns:* Increased risk of GH Increased risk of PAES Pregabalin *Concerns:* Increased risk of MCM Waiting for the first reproductive safety data, avoid milnacipran In patients with mild/moderate forms of the disorder: - CBT - U-ICBT - UB *Concerns:* Not tested in pregnant women Poor effective in patients with severe symptoms EU Independently of the severity of the disorder - CBT - U-ICBT - UB *Concerns:* Not tested in pregnant women Poor effective in patients with severe symptoms

CBT cognitive behavioral therapy, *U-ICBT* unguided internet cognitive behavioral therapy. *UB* unguided bibliotherapy, *GH* gestational hypertension, *PAES* Prenatal Antidepressant Exposure Syndrome, *MCM* major congenital malformations, *USA* United States of America, *EU* European Union

effect was unlikely to be independent from the drug effect on mood disorders, a frequent comorbid condition in patients with FMS. Importantly, there are still caveats on whether the observed results from pivotal studies were relevant and reasonably applicable to a European Union clinical setting. No demonstration on the long-term maintenance of the effect was provided. Thus, the Benefit/Risk ratio remains negative (EMEA 2008).

Waiting for the first reproductive safety data, milnacipram use should be avoided in pregnant women with FMS. Moreover, on 23 July 2009, the CHMP adopted a negative opinion, recommending the refusal of the EU marketing authorization for the medicinal product Milnacipran Pierre Fabre Médicament/Impulsor, intended for the treatment of FMS in adults. The main reasons which led to the negative opinion were the same reported for DUL (EMEA 2009).

With regards PGB, available data, albeit unconclusive, seem to suggest that the drug is not devoid of structural terogenicity potential. This finding is of particular concern. Indeed, reviewed studies show that a high proportion of pregnant women have been treated for disorders in which PGB is not officially approved. Off-label prescribing warrants particular attention and oversight when the drug use is not supported by scientific evidence showing greater benefits relative to risk (Dresser and Frader 2009). This is especially true in pregnancy. Imprudent drug use is a concern because it creates unnecessary costs and puts patients at risk of experiencing burdensome side effects and serious adverse events in mothers, fetuses, and newborns. For such reasons, the *over-causal handling*, off-label use of PBG in pregnancy must be strongly stigmatized and condemned. Moreover, on 23 April 2009, the CHMP adopted a negative opinion, recommending the refusal of an extension of indication that would include FMS treatment as a new indication for PGB. Pfizer requested a re-examination of the opinion. After considering the grounds for this request, the CHMP re-examined the initial opinion, and confirmed the refusal of the marketing authorization on 23 July 2009. The CHMP was concerned that the benefits of Lyrica ® in FMS had not been shown in either the short or the long term. There were no consistent or relevant reductions in pain or other symptoms in the short-term studies, and the maintenance of PGB effect was not shown in the longer study. The Committee was also concerned that the safety and effectiveness of PGB had not been shown in patients from the EU (Guzman 2018).

Conclusions

In the USA, PGB and DUL should be only given to women diagnosed with FMS complicated by depressive symptoms, showing severe symptomatological worsening during gestation (see Table 4), and after carefully weighing the benefits and risks for the mother-fetus dyad. Furthermore, all women requiring the use of should medications should be stringently monitored during pregnancy. Waiting for the first reproductive safety data, milnacipram use should be avoided during pregnancy.

In EU, no psychotropic medications have been approved for the treatment of FMS. Despite off-label prescribing is a common and legal practice in medicine, there are differences between countries in allowing the use of drugs beyond their own official indications. In the USA, this practice is justified when scientific evidence suggests the efficacy and safety of a medication for an indication for which it does not have FDA approval and when the practice is supported by expert consensus or practice guidelines (Furey and Wilkins 2016).

In European countries, such as Italy, the off-label use of medications is justified for drugs showing robust scientific evidence for their effectiveness in clinical situations for which the official approval is still lacking (Bollettino di informazione sui farmaci 2017). Moreover, clinicians have the ethical and legal duty to inform the patient that the prescribed drug is not officially approved for being used in its specific clinical condition (Bollettino di informazione sui farmaci 2017). Unfortunately, such conditions are not satisfied for any medications approved by the FDA for treating FMS. Indeed, as reported above, the CHMP stated that the short-term effect was not robustly demonstrated for both antidepressants and PGB. The CHMP also stated that no demonstration on the long-term maintenance of the effect was provided and that the Benefit/Risk ratio remains negative (EMEA 2008).

On the other hand, we have to consider that the proportion of women who discontinue psychotropic drugs and, specifically, antidepressant medications during pregnancy is as high as 85.4%. This figure raises further questions about adequate alternative treatment of FMS during the perinatal period (Zoega et al. 2015). Unfortunately, as reported above, psychological treatment of FMS in perinatal women is not yet tested (van Ravesteyn et al. 2017). Moreover, the effect sizes achieved by CBT are considerably lower than those achieved when treating other psychiatric disorder, such as anxiety disorders or depression (van Dessel et al. 2014; Kleinstäuber et al. 2011; Schröder et al. 2013). Heider et al. (2017) found that the poor response to CBT is related to high levels of precontemplation and the degree of symptom severity at baseline. Despite such limitations, in the light of the EMEA reports, European clinicians have no other instruments for treating FMS in pregnancy.

Waiting for more exhaustive efficacy and safety data, TMS should be avoided in pregnant women with FMS in both the USA and EU.

In the light of such considerations, the future direction of research in the field should be focused to definitively establish whether or not DUL, milnacipran, and DUL work effectively in FMS. Moreover, non-pharmacological interventions and, especially, CBT should be proved to be effective even during pregnancy.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

References

Abdy NA, Gerhart K (2013) Duloxetine withdrawal syndrome in a newborn. Clin Pediatr (Phila) 52:976–977

American Psychiatric Association (2013) Diagnostic and Statistical Manual of Mental Disorders, 4th edn. Arlington, VA, American Psychiatric Association

Atasever M, Namlı Kalem M, Sönmez Ç et al (2017) Lower serotonin level and higher rate of fibromyalgia syndrome with advancing pregnancy. J Matern Fetal Neonatal Med 30:2204–2211

Bellantuono C, Marini A, Lucarelli C (2013) Infant health and neurodevelopmental outcomes following prenatal exposure to duloxetine. Clin Drug Investig 33:685–688

Bérard A, Sheehy O, Zhao JP et al (2017) SSRI and SNRI use during pregnancy and the risk of persistent pulmonary hypertension of the newborn. Br J Clin Pharmacol 83:1126–1133

Bernardy K, Klose P, Welsch P et al (2018) Efficacy, acceptability and safety of cognitive behavioural therapies in fibromyalgia syndrome. A systematic review and meta-analysis of randomized controlled trials. Eur J Pain 22:242–260

Bidonde J, Busch AJ, van der Spuy I et al (2017) Whole body vibration exercise training for fibromyalgia. Cochrane Database Syst Rev 9: CD011755

Bollettino di informazione sui farmaci. (2017) http://www.agenziafarmaco.gov.it/wscs_render_attachment_by_id/111.285018.115401469992960af.pdf?id=111.285023.1154014700132. Accessed: September, 15, 2017

Boyce PM, Hackett LP, Ilett KF (2011) Duloxetine transfer across the placenta during pregnancy and into milk during lactation. Arch Womens Ment Health 14:169–172

Briggs GG, Ambrose PJ, Ilett KF et al (2009) Use of duloxetine in pregnancy and lactation. Ann Pharmacother 43:1898–1902

Brown HK, Ray JG, Wilton AS, Lunsky Y, Gomes T, Vigod SN (2017) Association between serotonergic antidepressant use during pregnancy and autism spectrum disorder in children. JAMA 317:1544–1552

De Ocampo MGP, Araneta MRG, Macera CA et al (2016) Risk of gestational hypertension and preeclampsia in women who discontinued or continued antidepressant medication use during pregnancy. Arch Womens Ment Health 19:1051–1061

Dresser R, Frader J (2009) Off-label prescribing: a call for heightened professional and government oversight. J Law Med Ethics 37:476–486

Einarson A, Smart K, Vial T, Diav-Citrin O, Yates L, Stephens S, Pistelli A, Kennedy D, Taylor T, Panchaud A, Malm H, Koren G, Einarson TR (2012) Rates of major malformations in infants following exposure to duloxetine during pregnancy: a preliminary report. J Clin Psychiatry 73:1471

EMEA. Refusal assessment report for Cymbalta (2008). http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000572/WC500076168.pdf. Accessed: February 16, 2018

EMEA. (2009) Milnacipran Pierre Fabre Medicament. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/001034/human_med_001311.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d125. Accessed: February 16, 2018

Eyal R, Yaeger D (2008) Poor neonatal adaptation after in utero exposure to duloxetine. Am J Psychiatry 65:651

Furey K, Wilkins K (2016) Prescribing "off-label": what should a physician disclose? AMA J Ethics 18:587–593

Gentile S (2015) Early pregnancy exposure to selective serotonin reuptake inhibitors, risks of major structural malformations, and hypothesized teratogenic mechanisms. Expert Opin Drug Metab Toxicol 11:1585–1597

Gentile S (2014) Anxiety and sleep disorders, psychopharmacology and pregnancy. In: psychopharmacology and pregnancy. Galbally, Snellen, and Lewis Edts. Springer Verlab, Berlin, pp 87–102

Gentile S (2012) Bipolar disorder in pregnancy: to treat or not to treat? The real question is how to treat most effectively. Br Med J 345: e7367. https://doi.org/10.1136/bmj.e7367

Gentile S (2010) On categorizing gestational birth, and neonatal complications following late in utero exposure to antidepressants. The prenatal antidepressant exposure syndrome. CNS Spectr 15:167–185

Guzman F. (2018) Pharmacology corner. Pregabalin (Lyrica) not approved for fibromyalgia by the EMEA. http://pharmacologycorner.com/pregabalin-lyrica-not-approved-fibromyalgia-emea/. Accessed: February 16, 201

Hedman E, Axelsson E, Andersson E, Lekander M, Ljótsson B (2016) Exposure-based cognitive-behavioural therapy via the internet and as bibliotherapy for somatic symptom disorder and illness anxiety disorder: randomised controlled trial. Br J Psychiatry 209:407–413

Heider J, Köck K, Sehlbrede M, Schröder A (2017) Readiness to change as a moderator of therapy outcome in patients with somatoform disorders. Psychother Res 28:722–733. https://doi.org/10.1080/10503307.2016.1265686

Henningsen P, Zipfel S, Sattel H et al (2018) Management of functional somatic syndromes and bodily distress. Psychother Psychosom 87: 12–31

Holland J, Brown R (2017) Neonatal venlafaxine discontinuation syndrome: a mini-review. Eur J Paediatr Neurol 21:264–268

Hoog SL, Cheng Y, Elpers J, Dowsett SA (2013) Duloxetine and pregnancy outcomes: safety surveillance findings. Int J Med Sci 10:413–419

Hudson JI, Wohlreich MM, Daniel K, Kajdasz DK (2005) Safety and tolerability of duloxetine in the treatment of major depressive disorder: analysis of pooled data from eight placebo-controlled clinical trials. Hum Psychopharmacol Clin Exp 20:327–341

Källén B, Borg N, Reis M (2013) The use of central nervous system active drugs during pregnancy. Pharmaceuticals 6:1221–1286

Khedr EM, Omran EAH, Ismail NM, el-Hammady DH, Goma SH, Kotb H, Galal H, Osman AM, Farghaly HSM, Karim AA, Ahmed GA (2017) Effects of transcranial direct current stimulation on pain, mood and serum endorphin level in the treatment of fibromyalgia: a double blinded, randomized clinical trial. Brain Stimul 10:893–901

Kleinstäuber M, Witthöft M, Hiller W (2011) Efficacy of short-term psychotherapy for multiple medically unexplained physical symptoms: a meta-analysis. Clin Psychol Rev 31:146–160

Knadler MP, Lobo E, Chappell J, Bergstrom R (2011) Duloxetine: clinical pharmacokinetics and drug interactions. Clin Pharmacokinet 50: 281–294

Kjaersgaard MI, Parner ET, Vestergaard M et al (2013) Prenatal antidepressant exposure and risk of spontaneous abortion: a population-based study. PLoS One 8:e72095

Kroenke K (2000) Somatoform disorders and recent diagnostic controversies. Psychiatr Clin North Am 30:593–619

Leo RJ, Brooks VL (2006) Clinical potential of milnacipran, a serotonin and norepinephrine reuptake inhibitor, in pain. Curr Opin Investig Drugs 7:637–642

Li F, Chin C, Wangsa J, Ho J (2012) Excretion and metabolism of milnacipran in humans after oral administration of milnacipran hydrochloride. Drug Metab Dispos 40:1723–1735

Liberati A, Altman DG, Tetzlaff J et al (2009) The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Ann Intern Med 151:W-65

Lupattelli A, Wood M, Lapane K, Spigset O, Nordeng H (2017) Risk of preeclampsia after gestational exposure to selective serotonin reuptake inhibitors and other antidepressants: a study from the Norwegian Mother and Child Cohort Study. Pharmacoepidemiol Drug Saf 26:1266–1276

Magtanong GG, Spence AR, Czuzoj-Shulman N, Abenhaim HA (2017) Maternal and neonatal outcomes among pregnant women with fibromyalgia: a population-based study of 12 million births. J Matern Fetal Neonatal Med Sep 27:1–7. https://doi.org/10.1080/14767058.2017.1381684

Medscape. News and perspectives. (2008) Cymbalta approved for fibromyalgia. https://www.medscape.org/viewarticle/576320. Accessed February 16, 2018

Medscape. News and perspectives. (2009) FDA approves milnacipran for fibromyalgia https://www.medscape.com/viewarticle/586898. Accessed: February 16

Mostacci B, Poluzzi E, D'Alessandro R, On behalf of the ESPEA Study Group et al (2018) Adverse pregnancy outcomes in women exposed to gabapentin and pregabalin: data from a population-based study. J Neurol Neurosurg Psychiatry 89:223–224

Newport JD, Hostetter AL, Juul SH et al (2016) Prenatal psychostimulant and antidepressant exposure and risk of hypertensive disorders in pregnancy. J Clin Psychiatry 77:1538–1545

Patorno E, Bateman BT, Huybrechts KF (2017) Pregabalin use early in pregnancy and the risk of major congenital malformations. Neurology 88:2020–2025

Saa'd S, Many A, Jacob G et al (2013) High prevalence of fibromyalgia symptoms among healthy full-term pregnant women. Rheumatol Int 33:1555–1560

Saltychev M, Laimi K (2017) Effectiveness of repetitive transcranial magnetic stimulation in patients with fibromyalgia: a meta-analysis. Int J Rehabil Res 40:11–18

Savella Pregnancy Registry (2009) https://clinicaltrials.gov/ct2/show/NCT01026077. Last update: September 22, 2016. Accessed: February 17, 2018

Schaefer KM (2004) Breastfeeding in chronic illness: the voices of women with fibromyalgia. MCN Am J Matern Child Nurs 29:248–253

Schröder A, Heider J, Zaby A et al (2013) Cognitive behavioral therapy versus progressive muscle relaxation training for multiple somatoform disorders: results of a randomized controlled trial. CognitTher Res 37:296–306

Stahl SM, Grady MM, Moret C, et al (2005) SNRIs: their pharmacology, clinical efficacy, and tolerability in comparison with other classes of antidepressants. CNS Spectr 10:732–747

Sujan AC, Rickert ME, Öberg SA et al (2017) Associations of maternal antidepressant use during the first trimester of pregnancy with preterm birth, small for gestational age, autism spectrum disorder, and attention-deficit/hyperactivity disorder in offspring. JAMA 317: 1553–1562

Sujan AC, Öberg AS, Quinn PD, D'Onofrio BM (2018) Annual Research Review: Maternal antidepressant use during pregnancy and offspring neurodevelopmental problems - a critical review and recommendations for future research. J Child Psychol Psychiatry. https://doi.org/10.1111/jcpp.13004

Tassone DM, Boyce E, Guyer J, Nuzum D (2007) Pregabalin: a novel gamma-aminobutyric acid analogue in the treatment of neuropathic pain, partial-onset seizures, and anxiety disorders. Clin Ther 29:26–48

Temple University (2006) Fibromyalgia increases pain and fatigue for pregnant women. ScienceDaily. ScienceDaily, 5. www.sciencedaily.com/releases/2006/07/060705184726.htm. Accessed: September 20, 2017

Trivedi MH, Desaiah D, Ossanna MJ et al (2008) Clinical evidence for serotonin and norepinephrine reuptake inhibition of duloxetine. Int Clin Psychopharmacol 23:161–169

Tulay KT, Emrullah T, Aydin A et al (2016) The effect of fibromyalgia syndrome to gravidity, parity and duration of breastfeeding; a prospective study from Turkey. Pak J Med Sci 32:545–549

van Dessel N, den Boeft M, van der Wouden JC et al (2014) Onpharmacological interventions for somatoform isorders and medically unexplained physical symptoms (MUPS) in adults. Cochr Database System Rev 11:CD011142

van Ravesteyn LM, Lambregtse-van den Berg MP, Hoogendijk WJP et al (2017) Interventions to treat mental disorders during pregnancy: a systematic review and multiple treatment meta-analysis. PLoS One 12:e0173397

Weiss N, Ivanova E (2008) Does the voltage-gated calcium channel alpha2delta-1 subunit play a dual function in skeletal muscle? J Physiol 586:2035–2037

Winterfeld U, Merlob P, Baud D, Rousson V, Panchaud A, Rothuizen LE, Bernard N, Vial T, Yates LM, Pistelli A, Ellfolk M, Eleftheriou G, de Vries LC, Jonville-Bera AP, Kadioglu M, Biollaz J, Buclin T (2016) Pregnancy outcome following maternal exposure to pregabalin may call for concern. Neurology 86(24):2251–2257. https://doi.org/10.1212/WNL.0000000000002767

Wolfe F, Clauw DJ, Fitzcharles MA et al (2011) Fibromyalgia criteria and severity scales for clinical and epidemiological studies: a modification of the ACR Preliminary Diagnostic Criteria for Fibromyalgia. J Rheumatol 38:1113–1122

Wolfe F, Wallitt BT, Katz RS et al (2014) Symptoms, the nature of fibromyalgia, and Diagnostic and Statistical Manual 5 (DSM-5) defined mental illness in patients with rheumatoid arthritis and fibromyalgia. PLoS One 9:e88740

Zioni T, Buskila D, Aricha-Tamir B, Wiznitzer A, Sheiner E (2011) Pregnancy outcome in patients with fibromyalgia syndrome. J Matern Fetal Neonatal Med 24:1325–1328

Zoega H, Kieler H, Nørgaard M, Furu K, Valdimarsdottir U, Brandt L, Haglund B (2015) Use of SSRI and SNRI antidepressants during pregnancy: a population-based study from Denmark, Iceland, Norway and Sweden. PLoS One 10:e0144474