Eur J Pediatr (2016) 175:9–18
DOI 10.1007/s00431-015-2670-x

REVIEW

Psychotropic treatments in Prader-Willi syndrome: a critical review of published literature

O. Bonnot[1] · D. Cohen[2] · D. Thuilleaux[3] · A. Consoli[2] · S. Cabal[5] · M. Tauber[4]

Received: 4 August 2015 / Revised: 4 November 2015 / Accepted: 12 November 2015 / Published online: 19 November 2015

Abstract Prader-Willi syndrome (PWS) is a rare genetic syndrome. The phenotype includes moderate to intellectual disability, dysmorphia, obesity, and behavioral disturbances (e.g., hetero and self-injurious behaviors, hyperphagia, psychosis). Psychotropic medications are widely prescribed in PWS for symptomatic control. We conducted a systematic review of published literature to examine psychotropic medications used in PWS. MEDLINE was searched to identify articles published between January 1967 and December 2014 using key words related to pharmacological treatments and PWS. Articles with original data were included based on a standardized four-step selection process. The identification of studies led to 241 records. All selected articles were evaluated for case descriptions (PWS and behavioral signs) and treatment (type, titration, efficiency, and side effects). Overall, 102 patients were included in these studies. Treatment involved risperidone (three reports, $n=11$ patients), fluoxetine (five/$n=6$), naltrexone (two/$n=2$), topiramate (two/$n=16$), fluvoxamine (one/$n=1$), mazindol (one/$n=2$), *N*-acetyl cysteine (one/$n=35$), rimonabant (one/$n=15$), and fenfluramine (one/$n=15$).

Conclusion: We identified promising treatment effects with topiramate for self-injury and impulsive/aggressive behaviors, risperidone for psychotic symptoms associated with uniparental disomy (UPD), and *N*-acetyl cysteine for skin picking. The pharmacological approach of behavioral impairment in PWS has been poorly investigated to date. Further randomized controlled studies are warranted.

What is Known:
- *Behavioral disturbances in Prader-Willi syndrome including aggressive reactions, skin picking, and hyperphagia might be very difficult to manage.*
- *Antipsychotic drugs are widely prescribed, but weight gain and increased appetite are their major side effects.*

What is New:
- *Topiramate might be efficient for self-injury and impulsive/aggressive behaviors, N-acetyl cysteine is apromising treatment for skin picking and Antidepressants are indicated for OCD symptoms.*
- *Risperidone is indicated in case of psychotic symptoms mainly associated with uniparental disomy.*

Keywords Prader-Willi syndrome · Antipsychotic · Topiramate · Risperidone · Methylphenidate · Antidepressor

Communicated by Jaan Toelen

✉ O. Bonnot
olivier.bonnot@chu-nantes.fr

D. Cohen
david.cohen@psl.aphp.fr

D. Thuilleaux
denise.thuilleaux@hnd.aphp.fr

A. Consoli
angele.consoli@psl.aphp.fr

S. Cabal
cabal-berthoumieu.s@chu-toulouse.fr

M. Tauber
tauber.mt@chu-toulouse.fr

[1] Child and Adolescent Psychiatry Department, LPL-University Hospital Nantes and GDR 3557, Psychiatric Institute, 7 quai Moncousu, Nantes F-44 000, France

[2] Child and Adolescent Psychiatry Department, Groupe Hospitalier Pitie Salpetriere, APHP, Paris & Centre for Rare Diseases with Psychiatric Symptoms, APHP, 47 boulevard de l'hôpital, Paris 75013, France

[3] Rare Disease with Psychiatric Symptoms Department, Hôpital Mari, APHP, Route de la Corniche, Hendaye 64700, France

[4] Pediatric Department, University Hospital Toulouse & Rare Disease Center for Prader Willi Syndrome, CHU de Toulouse, Toulouse, France

[5] Child and Adolescent Psychiatry Department, CHU de Toulouse, Toulouse, France

Abbreviations

ABC	Aberrant behavior checklist
CBT	Cognitive behavioral therapy
CGI	Clinical global impression
DEL	Deletion
OCD	Obsessive compulsive behavior
ROAS	Retrospective overt aggressive score
SIRCL	Self-injury restraint checklist
UPD	Uniparental disomy
YBC-OC	Yale Brown obsessive compulsive subscale

Introduction

Patients with a rare disease are often challenging to treat when considering psychotropic treatment for behavioral or psychiatric manifestations. There is an important lack of clear data or treatment guidelines for treating behavioral disturbance in patients with intellectual disabilities. Prader-Willi syndrome (PWS) is a paradigmatic example of such a disease. It is a rare disease with an estimated prevalence of 1:25,000 at birth [40]. PWS is a genetic disease located on chromosome 15 (15 q11–q13). Imprinting silences the maternal genes on 15 q11–q13, rendering them non-functional, with the paternal non-imprinted genes being absent. Approximately 60 to 70 % of patients with PWS have a paternal deletion of 15 q11–q13 [12]. An additional 25 to 35 % of patients have two copies of maternal chromosome 15 (uniparental disomy (UPD)). Rarely, PWS may be associated with translocation, mutation, or other anomalies [12]. Angelman syndrome, which has primarily been associated with autism spectrum disorders, involves the same genetic region and is commonly associated to mutations of the maternal allele of the UB3a gene or rare deletions.

PWS patients present in a neonatal hypotonic state with deficit of sucking and eating refusal which progresses to with hyperphagia and obsession with food in early childhood. In addition, patients have distinct facial features, such as a narrow forehead, almond-shaped eyes, and a triangular mouth, as well as a short stature, related to growth hormone deficiency and small hands and feet. Puberty is often delayed or incomplete, and most affected individuals are unable to have children. This eating disorder is more similar to an addictive disorder to food than a traditional eating disorder [21]. PWS leads to severe obesity, which is a major issue associated with quality of life and medical prognosis.

Psychiatric and cognitive symptoms in patients with PWS are severe and have an important impact on social and interpersonal life [53]. Patients with PWS often have mild to moderate intellectual disability (ID) [28], with learning impairments and poor academic achievement [59]. They have particular difficulties in mathematics, calculation, and abstraction [9], which may be related to under-diagnosed neurovisual impairments [46]. There is a large individual heterogeneity of language impairments, primarily in morphosyntaxic abilities [56]. Behavioral impairments predominately include temper outbursts, impulsivity, emotional liability, and aggressive behavior [7, 21], as well as self-injury behavior, such as compulsively picking the skin and mucosa (rectal picking), which may lead to a severe wound and severe infections [37]. Patients with UPD as a group have more psychiatric illness and autism symptoms and exhibit more severe overall symptoms than patients with a deletion; however, they seem to have less skin picking and even better expressive language [21]. Measures of maladaptive behavior, compulsive behavior, hyperphagia, and adaptive behavior were statistically similar between the groups [21].

Regarding the relationship between PWS and schizophrenia spectrum disorders (SSDs), five studies have utilized standardized psychometric tools to assess psychiatric diagnoses [6, 11, 49, 50, 57]. Vogels and colleagues reported that psychotic episodes, which occur in 16 % of individuals with PWS, had an onset in adolescence, never occurred in individuals with deletion, and were exclusively associated with UPD or imprinting abnormalities [57]. A recent study showed that in the case of UPD, approximately all individuals with histories of psychopathology suffered from psychotic symptoms (85 %) with or without an affective component [49]. Boer and colleagues reported that 7 of 25 patients with UPD aged 18 years or older had a severe affective disorder with psychotic features, with a mean age of onset of 26 years (SD 5.9) [11]. SSDs are primarily, but not exclusively, associated with UPD, and the clinical diagnosis may be complicated. Indeed, auditory hallucinations have been reported on questionnaires provided to parents or caregivers and have been identified in 12 of 35 young adults with PWS [58] and in 14 of 95 patients of various ages [14].

Patients with deletion (DEL) present more psychiatric features (17 % of them) than those with UPD {Beardsmore, 1998 #12; Sinnema, 2011 #15}. A majority (56 % of all patients with psychiatric symptoms) exhibits psychotic features. Depressive mood is the most common psychiatric symptom. It is therefore important to search for psychotic feature in depressive PWS patients. The total of PWS patients with DEL having psychotic symptoms might be estimated around 9 % {Sinnema, 2011 #15}.

Review scope

Psychotropic medications are often administered to patients to control the behavioral disturbances associated with PWS or to treat comorbid SSDs and/or depression. Despite a large network of reference center for rare disease, it is well known that patients with intellectual disabilities and mental disorders have a lower access to specialists than other patients. Patients with PWS may possibly be examined by practitioners with general

practice practitioners, psychiatrists, or endocrinologist for example. When it comes to behavioral disturbances, medication is often an option and information regarding efficiency of different treatments is difficult to obtain. We aimed to conduct a systematic review of published literature to examine the psychotropic medications used in PWS. We choose to limit to published literature in medical database on purpose as our point was also to point out the necessity of gold standard psychopharmacological studies in this field.

Experimental procedure

The rare disease program in France was initiated in 2007 and led to the creation of more than 200 National Reference Centers. One center in Toulouse is dedicated to PWS (from 2004), and one center in Paris (from 2007) is dedicated to psychiatric symptoms of rare diseases, including PWS. Clinicians and researchers of these two national reference centers collaborated for this review.

Literature search methodology and data sources

The public MEDLINE database was searched according to a standard four-step protocol, which is described in the following sections and summarized in Fig. 1.

Identification The search used EndNote X7 software (Thomson Reuters), which enabled the identification and deletion of duplicate records. Relevant publications from January 1968 to January 2014 (which is PubMed NLM database date range) were identified. The key words included psychotropic, antipsychotic, neuroleptic, stimulant, methylphenidate, mood stabilizer, antiepileptic, antihistaminic, antidepressant, behavioral treatment, associated with Prader-Willi syndrome (and all truncated versions). A total of 275 potentially relevant articles were identified within ten separate EndNote databases, one of which was created for each class of treatment/compounds as follows (*n* indicates the numbers of articles found using each key word): psychotropics ($n=10$), antipsychotics ($n=11$), neuroleptics ($n=5$), stimulants ($n=8$), methylphenidate ($n=3$), mood stabilizers ($n=0$), anticonvulsants ($n=16$), antihistaminics ($n=0$), antidepressants ($n=17$), and behavioral treatments ($n=205$). After the records were searched for duplicates, 241 publications were collated for screening.

Screening Two groups worked separately to screen the abstracts of relevant articles (group 1: S. Cabal, A. Consoli, and D. Cohen; group 2: O. Bonnot, M. Tauber, and D. Thuilleaux). All articles that contained relevant data regarding treatment efficacy in patients with PWS and behavioral issues or psychiatric symptoms were selected. Articles were excluded from the full-text analysis (see "Eligibility" stage) according to the following exclusion criteria: (1) articles in which no data were available regarding efficacy or articles with insufficient information regarding the case; (2) unrelated articles, despite the inclusion of a key word; (3) literature reviews that did not contain original data; and (4) articles that included data previously reported elsewhere. The screening excluded 199 of the initial publications. We kept all non-excluded article. In cases where the two analysis groups did not agree, records were maintained and included in the next step.

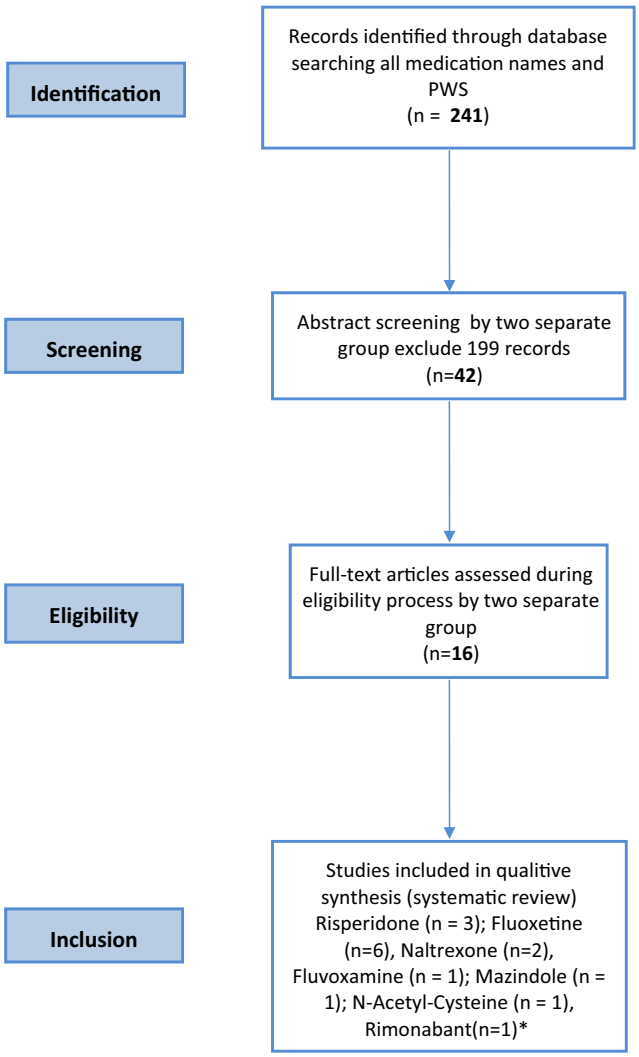

Fig. 1 Diagram flow of identification, screening, eligibility, and inclusion for our systematic review of treatment for behavioral disorders in Prader-Willi syndrome. The *asterisk* indicates that total is over 16 due to multiple cases in some publications

Eligibility The same two analysis groups accessed the full texts of all remaining articles ($n=42$) and determined their further eligibility according to the same exclusion criteria used in the abstract screening stage. Numerous articles ($n=15$) provided information regarding treatment in large case series but did not include details regarding efficacy or tolerance. Three

articles reported the results of a short-term (few hours) trial of naltrexone [32], benzodiazepines [22], or medications for sleep disturbances [33] and were not included. We also did not include articles related to the effects of growth hormone (for a review, see [13]). Sixteen articles remained after eligibility screening.

Results

The main results (study design, demographics, clinical data, efficacy, and side effects) are summarized in Table 1. Most studies are regarding adolescents and young adults. We identified studies that reported the effects of risperidone (n=3), fluoxetine (n=6), naltrexone (n=2), fuvoxamine (n=1), mazindole (n=1), *N*-acetyl cysteine (n=1), rimonabant (n=1), and topiramate (n=2). The total number of studies here exceeds 16 because multiple cases were reported in some publications. The studies were very heterogeneous with respect to the treatment used and the symptom targets. Overall, the analysis included 103 patients and two randomized controlled trials (RCTs). One study used an original design with discontinuation treatment to demonstrate the efficacy of treatment and a worsening of symptoms during the discontinuation period [27]. Statistical analysis results were not available for the majority of articles mainly because of the small sample size. As all the co-authors are professional in the field of PWS, we had a consensus appreciation of the results and data given by the article.

In all but six articles [3, 26, 36, 47, 48, 51], there was no information regarding the genetic mechanism of the chromosomal abnormality carried by the patients. Additionally, we identified an IQ evaluation in only three articles [5, 31, 44]. The durations of the trials were longer than average for short-term studies because all but three articles had a follow-up period greater than 3 months. Most studies that utilized common SPW programs were still running during the trial. These programs are poorly described but mostly based on behavioral food control.

Reports regarding the efficacies of treatments were heterogeneous, ranging, for example, from a very precise description of size and number of skin pickings with pictures to subjective affirmation.

The assessment of behavior was also widely heterogeneous. The use of a psychometric scale or questionnaire was scarce. Regarding the assessment of aggressive behavior, three studies used the retrospective overt aggressive score [3, 19, 20], two studies used the clinical global impression (CGI), and two studies used the aberrant behavior checklist [47, 48]. No study used scales for eating behavior. Most of the studies that focused on food intake, eating behavior, or hyperphagia employed absolute weight measurement.

Few studies assessed all the main aspects of behavioral efficiency of patients.

Two studies assessed all aspects of behavior (eating, obsessive compulsive behavior (OCD), aggression, and self-injury) [47, 51], and the other studies focused on one to three components.

Discussion

The literature on psychotropic treatments in individuals with PWS is scarce, and the strength of the studies is questionable. With the exception of case reports, we identified eight studies [19, 20, 27, 36, 38, 45, 47, 51], including two RCTs [38, 45]. One RCT compared the study drug with placebo [38]. Our review raises more questions than answers. Antipsychotics and selective serotonin reuptake inhibitors (SSRIs) are the most studied treatments, while promising therapeutic options must be further explored. Our choice was to limit our review to medical database published literature. This is a clear limitation, but "gray literature," which is useful in this case, must be examined by consensus representative group work to avoid bias and was not possible.

Antipsychotics

Antipsychotics are a frequent pharmacological option in patients with intellectual disability [15] and those with PWS. We identified reports of improvement in four cases [3, 20] and in an open-label trial [20]. However, these data were not sufficiently strong (sample size and experimental design mainly) to challenge the numerous data regarding antipsychotics in adults [18] and children/adolescents [15] with intellectual disabilities or genetic diseases with psychiatric symptoms. These general data repeatedly showed that weight gain with antipsychotics (APs), especially risperidone (main AP used in PWS patients), was important; furthermore, the mechanism associated with weight gain, which is partly unknown, is linked to an augmentation of appetite. Moreover, the literature indicates that the efficacy of APs with respect to behavioral issues is weak in patients with an intellectual disability, and data on this topic are scarce [25, 55]. It is remarkable and surprising that in the three articles we found regarding risperidone and PWS, results suggest a positive effect on weight and appetite {Araki, 2010 #28; Durst, 2000 #33; Durst, 2000 #34}. These results, if confirmed in larger sample, could suggest that mechanisms involved in increase of appetite in PWS are different than those of AP and/or are not affected by AP drugs. Physiological and clinical studies are necessary that may lead to a better understanding of both mechanisms.

In addition to behavioral issues, APs may be useful for psychotic symptoms. Patients with PWS, especially UPD subjects, are at risk for SSDs and mood disorders [6, 11, 49, 50, 57]. Antipsychotics are the gold standard in the treatment of SSDs, and some authors have suggested that APs protect

Table 1 Main characteristics of case reports and studies on Prader-Willi syndrome and pharmacological treatment

Reference	Type (*n*)	Gender (*n*)	Genetic type	IQ	Age	Follow-up	Treatment (dose)	Therapy	Efficiency				Side effects
									Eating behavior (weight)	Skin picking	OCD	Aggressive behavior	
[16]	Case report (1)	F (1)	–	–	17	6 months	Fluoxetine 40 mg/day	Calories control	Improvement (199 to 193 lbs)	No change	–	Improvement	None reported
[8]	Case report (1)	F (1)	–	–	9	1 year	Fluoxetine 60 mg/day + naltrexone 60 mg/day	Calories control	Improvement (−1 kg)	No change	–	Improvement	None reported
[44]	Case report (2)	M (2)	–	57–70	18–21		Fluoxetine 40–60 mg/day		No change	No change			Diabetes (1)
[31]	Case report (1)	M (1)	–	67	14	2 weeks (expected 6-week trial)	Fluvoxamine (50–200 mg/day)	Token reward program	Worsening (+3 kg)	No change	Improvement	Worsening	None reported
[31]	Case report (1)	M (1)	–	67	14	2 weeks (expected 6-week trial)	Fluoxetine 60 mg/day	None reported	Worsening	No change	Improvement	Worsening	None reported
[1]	Case report (1)	F (1)	UPD		13	3 weeks	Fluoxetine 10 mg/day		No change	No change			Psychosis
[3]	Case report (1)	M (1)	DEL	–	11	18 months	Risperidone (0.5–1.5 mg/day)	Cbt	Improvement (120 to 80 kg)	None reported		Improvement (ROAS)	None reported
[5]	Case report (1)	M (1)	–	65	15	15 months	Naltrexone 50 mg/day	Common behavioral therapy	–	Improvement	–	–	–
[27]	Prospective open-label trial discontinued (2)	F (2)	–	–	11–14	40 weeks (24-weeks with treatment)	Mazindol (1–2 mg/day)	Common behavioral therapy	Improvement (−10 and 9.8) with 50 % regained in discontinuation period	None reported	None reported	None reported	None reported
[19]	Prospective open-label trial (3)	M (3)	–	–	18–21	37 weeks	Risperidone (1 to 2 mg/day)	None reported	Improvement for two (−9.5 and 12.5 kg) and gain for one (+4 kg but recent surgery)	None reported		Improvement (ROAS and CGI)	None reported
[20]	Prospective open-label trial (7)	M (5) F (2)	–		15–15	37 weeks	Risperidone (0.5–3 mg/day)	Common behavioral therapy	Improvement (5/7=−10.9 kg) worsening (2/7=+3 kg)	None reported	Improvement	Improvement (ROAS and CGI)	None reported
[47]	Prospective open-label trial (8)	M (5) F (3)	DEL (6) UPD (2)		19–38	8 weeks	Topiramate (125–200 mg/day)	Calorie control and food restriction	No change	Improvement (SIRCL list, p=0.006)	No change (YBC-OC)	Improvement (ABC p=0.03)	None reported
[51]	Prospective open-label trial (8)	F 4) M (4)	DEL (5) UPD (2) RT (1)		10–19	1 year	Topiramate (100–600 mg/day)	Common behavioral therapy	Improvement for three, moderate for two, worsening for two (−3 kg for four; +4 kg for three)	Improvement for two, modest improvement for two, worsening for one patient	Improvement	Improvement	None reported
[36]	Prospective open-label trial (39)	M (23) F (12)	DEL (24) UPD (11)		5–39	12 weeks	*N*-acetyl cysteine (450–1200 mg/day)	None reported	–	Improvement for all and 71 % with complete	–	–	None reported

Table 1 (continued)

Reference	Type (*n*)	Gender (*n*)	Genetic type	IQ	Age	Follow-up	Treatment (dose)	Therapy	Efficiency				Side effects
									Eating behavior (weight)	Skin picking	OCD	Aggressive behavior	
[45]	Double-blind placebo trial (15)	M (7) F (8)	–	–	5.5–27	6-week treatment, 6-week placebo (two groups)	Fenfluramine 30, 60, 120 mg/day (5–7, 7–15, and over 15 years old, respectively)	None reported	Improvement ($p<0.05$) and weight loss for 8 treated vs 2 in placebo group; $p=0.02$)	remission (nb of lesions and size) Improvement in self direct behavior ($p<0.025$)	–	Improvement in aggressive behavior ($p<0.05$)	None reported
[38]	Double-blind placebo trial (15)	–	–	–	19–36	6 months	Rimonabant 20 mg/day	–	Improvement (95 to 77 kg) vs no change in placebo group	–	–	No change	Anxiety, delusion, and dysthymia leading to 50 % withdrawal

OCD obsessive compulsive behavior, *None reported* absence of variable specifically indicated in the article, *ROAS* retrospective overt aggressive score, *SIRCL* self-injury restraint checklist, *ABC* aberrant behavior checklist, *YBC-OC* Yale Brown obsessive compulsive subscale, *CGI* clinical global impression, *UPD* uniparental disomy, *DEL* deletion, *CBT* cognitive behavioral therapy

patients with previous psychotic symptoms from relapse [53]. It is unknown whether there is a protective effect of APs in UPD patients who have not previously exhibited psychotic signs. One large epidemiological study of a sample of 156 patients demonstrated that a subgroup of patients treated with APs, regardless of their genetic status and history of previous psychotic episodes, was less likely to develop a psychiatric illness during the 2.5-year follow-up period [53]. Interestingly, patients with no previous psychotic episodes also presented fewer psychotic episodes during the follow-up compared with patients not treated with AP. However, this study was naturalistic, and the patients had various treatments and courses of psychiatric diseases and symptoms. SSDs are very difficult to diagnose in PWS patients because of their tendency to fabulation, or make up stories, and the associated intellectual deficiencies [53]. Decreasing the transition rate for psychotic symptoms in high-risk SSD patients is a major research area in psychiatry. After several years of controversy, a consensus has been reached to restrict treatment to patients who have or have had psychotic symptoms (for a critical review, see [23]).

RCT studies are necessary to estimate the benefit/risk ratio of AP in PWS patients. To date, main indication in PWS for AP is to target existing psychotic symptoms as studies suggests that the negative effects of these medications may not be outweighed by the clinical benefits.

Selective serotonin reuptake inhibitors

SSRIs are the second most prescribed psychotropic treatment in PWS patients according to our systematic review. The rationale is that SSRIs are known to induce a decrease in appetite and are effective for OCD. We found similar results in patients with an improvement in OCD, but the findings were derived from only two cases [31]. SSRIs were found to be effective for eating disorders in only one case [16]. However, the studies were weak with respect to design (no placebo, primarily retrospective and case reports). SSRIs may not be indicated for core behavioral symptoms in PWS patients, at this time. They might, however, be indicated for OCD in this population.

As previously said, patients with PWS, especially those with DEL, have a vulnerability to depression {Sinnema, 2011 #15; Skokauskas, 2012 #16; Soni, 2007 #57}. We found no studies dedicated, or assessing, depressed mood. Studies in this field, especially to assess efficiency of AD drugs and psychotherapeutic programs (i.e., cognitive and behavioral therapy, support therapy…) are necessary in this population.

Naltrexone

Only one case study concerns the use of naltrexone in PWS [5] showing a poor efficiency. One article is concerning naltrexone associated with fluoxetine with moderate

improvement in eating behavior and aggressive behavior [8]. This result may be compared to a recent review regarding self-injury behavior in patients with ID failed to demonstrate an efficacy of pharmacological treatment, especially clomipramine and naltrexone [41].

Topiramate

Topiramate is an antiepileptic mood stabilizer used for antiimpulsivity [17, 43]. The major side effect is loss of appetite, and it has also been indicated for morbid obesity. Topiramate has been prescribed for the treatment of eating disorders [29, 42]. In a recent meta-analysis that pooled five randomized controlled trials of bulimia nervosa (n=128) and binge eating disorder (n=528), topiramate was more efficient in reducing the quantity of binges, the frequency of "loss of control" (binge), and weight compared with placebo [4].

Treatment with topiramate appears to be promising in PWS patients. The two studies conducted were prospective, and the assessments were psychometric and rated; the studies assessed all behavioral symptoms of PWS patients. The follow-up in one study was 1 year [51], while that in the other study was 8 weeks [47]. Interestingly, while only one study report improvement in eating behavior, both studies provide support for the efficacy of topiramate in improving eating behavior [51], impulsivity, aggressive behavior, and skin picking. The results for OCD were weak because only one study used a specific scale to assess OCD, and it showed no improvement. Topiramate is also often used in specialized centers for PWS.

Data regarding the side effects are poor in PWS, but topiramate has been shown to induce hallucination in 2–5 % of treated patients [30, 34, 35, 39, 54]; this side effect may be of particular importance in PWS, especially for patients with UPD.

Because of the theoretical and known clinical efficacy, it is of particular importance to conduct RCTs of topiramate in PWS patients, with cautious recording of the side effects in this population. To date, topiramate appears to be one of the most promising treatments.

Fenfluramine and rimonabant

Fenfluramine, a central anorexigen drug, has shown efficacy in a double-blind controlled placebo trial (n=15) for eating behavior, weight, and aggressive behavior [45]. The sample was small, and the side effects were not reported. However, the Food and Drug Administration and the European Medicines Agency announced the withdrawal of fenfluramine in the late 1990s because of the risk of cardiac valvular disease. In 2008, the endocannabinoid CB1 receptor antagonist rimonabant was withdrawn from the European market. The drug reduced appetite and produced significant weight loss, but it increased the risk of anxiety and depressive disorders, including suicidality. We identified one RCT with rimonabant that showed improvement in weight loss, as well as anxiety disorders, mood disorders, and delusions [38].

Stimulants and *N*-acetyl cysteine

Surprisingly, we only identified one trial with a small sample (n=2) and no psychometric assessment regarding treatment with stimulants. Two prospective cases with mazindol demonstrated improvements in eating behavior and weight. These cases were poorly described and may not be considered trials; however, a stimulant of the central nervous system, such as methylphenidate, may potentially be efficient in the treatment of core psychiatric symptoms of PWS because of the drug's effects on aggressive behavior and impulsivity and the known side effect on decreasing appetite [10]. However, side effects of stimulant, especially slowing growth and anxiety, should be carefully monitored if RCTs of stimulants are conducted in younger patients with PWS.

One recent study examined the use of *N*-acetyl cysteine for self-injury behavior, especially skin picking, in 35 patients with PWS [36]. The results were evaluated based on the number and size of the lesions (with pictures) and suggest a remarkable efficacy after 12 weeks of treatment. This is the first and only study to use this medication in PWS. The main aim was to compare skin pricking with OCD behavior in patients with PWS. Glutamate is involved in OCD [60], and recent research suggests that *N*-acetyl cysteine supports the body's antioxidant and nitric oxide systems during stress, infections, toxic assault, and inflammatory conditions, most likely via modulation of NMDA glutamate receptors or by increasing glutathione [2]. Further controlled studies with a placebo group and larger sample are needed to verify these promising results.

Finally, we know that the course and severity of PWS in patients with DEL or UPD is different, especially with respect to psychiatric aspects and cognitive functioning. UPD patients exhibit a more severe disease course [24, 52]. It is particularly unfortunate that most articles did not provide precise descriptions regarding this point and that, when it was documented, no details were provided regarding the treatment response in patients.

Further studies in this field are necessary and should be based on solid baseline and endpoint evaluation using general assessment scale, such as CGI (used in many RCT) and behavioral scales such as aberrant behavior checklist. It is also necessary to use specific PWS scales such as the Dykens questionnaire, especially oriented for PWS patients and eating behaviors {Dykens, 2007 #5}.

Conclusion

PWS represents a good example of a genetic disease with behavioral and psychiatric symptoms that may be challenging to treat with psychotropic medications. Hyperphagia and

obesity are the primary symptoms of this disease. Unfortunately, antipsychotics, which are widely prescribed for intellectually deficient patients with aggressive behavior and impulsivity, induce a widely documented increase in appetite with subsequent weight gain. Our systematic review of psychotropic mediation in PWS patients with behavioral and psychiatric symptoms indicates a poor literature base with few controlled trials and many case reports. However, the review identified some promising treatments, such as topiramate and *N*-acetyl cysteine, which require large-sample RCTs to assess the efficacy and precisely evaluate the side effects of these medications. Future RCT in this field are therefore needed. Antidepressants may also be useful in the case of comorbid OCD, and this should be assessed in clinical trials also (for OCD and depression). The organization of large registers of patients, which has been initiated, and the well-organized association of patients with this disease could facilitate recruitment in future studies [24].

Authors' contribution OB, DC, and MT conceived of the study and participated in its design and coordination and helped to draft the manuscript. DC made the most important contribution to this second part. All authors (OB, DC, AC, SC, DT, and MT) did participate in the meetings regarding the bibliography search, the reading of the selected articles, and the related discussions. OB, DC, DT, and MT participated in the design of the study. All authors read and approved the final manuscript.

Compliance with ethical standards Research is not involving human participant.

This article does not contain any studies with human participant performed by any of the authors. There is no human or animal material use in this study and no personal data of any kind. Our work is entirely based on literature search.

Informed consent Informed consent was not relevant. No informed consent.

Conflict of interest The authors declare that they have no competing interests.

Funding This study was funded by a Grant of French Ministry of Health (PHRC 2010-AOM1008).

Information's regarding authors We are a group of psychiatrists and pediatrician implicated in rare disease with psychiatric symptoms, including PWS. We are working in a national reference network in this field funded by the French government and European Union. MT, DT, and SC are working in the National Reference Center for PWS, and OB, DC, and AC are working in the National Reference Center for Psychiatric Symptoms of Rare Disease.

References

1. Adams S, Penton-Voak IS, Harmer CJ, Holmes EA, Munafo MR (2013) Effects of emotion recognition training on mood among individuals with high levels of depressive symptoms: study protocol for a randomised controlled trial. Trials 14:161. doi:10.1186/1745-6215-14-161
2. Amrouche-Mekkioui I, Djerdjouri B (2012) N-acetylcysteine improves redox status, mitochondrial dysfunction, mucin-depleted crypts and epithelial hyperplasia in dextran sulfate sodium-induced oxidative colitis in mice. Eur J Pharmacol 691:209–217. doi:10.1016/j.ejphar.2012.06.014
3. Araki S, Ohji T, Shiota N, Dobashi K, Shimono M, Shirahata A (2010) Successful risperidone treatment for behavioral disturbances in Prader-Willi syndrome. Pediatrics international : official journal of the Japan Pediatric Society 52:e1–e3. doi:10.1111/j.1442-200X.2009.02996.x
4. Arbaizar B, Gomez-Acebo I, Llorca J (2008) Efficacy of topiramate in bulimia nervosa and binge-eating disorder: a systematic review. Gen Hosp Psychiatry 30:471–475
5. Banga A, Connor DF (2012) Effectiveness of naltrexone for treating pathologic skin picking behavior in an adolescent with Prader-Willi syndrome. J Child Adolesc Psychopharmacol 22:396–398. doi:10.1089/cap.2012.0028
6. Beardsmore A, Dorman T, Cooper SA, Webb T (1998) Affective psychosis and Prader-Willi syndrome. J Intellect Disabil Res 42(Pt 6):463–471
7. Benarroch F, Hirsch HJ, Genstil L, Landau YE, Gross-Tsur V (2007) Prader-Willi syndrome: medical prevention and behavioral challenges. Child Adolesc Psychiatr Clin N Am 16:695–708. doi:10.1016/j.chc.2007.03.007
8. Benjamin E, Buot-Smith T (1993) Naltrexone and fluoxetine in Prader-Willi syndrome. J Am Acad Child Adolesc Psychiatry 32:870–873. doi:10.1097/00004583-199307000-00025
9. Bertella L, Girelli L, Grugni G, Marchi S, Molinari E, Semenza C (2005) Mathematical skills in Prader-Willi Syndrome. J Intellect Disabil Res 49:159–169
10. Biederman J, Faraone SV (2005) Attention-deficit hyperactivity disorder. Lancet 366:237–248. doi:10.1016/S0140-6736(05)66915-2
11. Boer H, Holland A, Whittington J, Butler J, Webb T, Clarke D (2002) Psychotic illness in people with Prader Willi syndrome due to chromosome 15 maternal uniparental disomy. Lancet 359:135–136
12. Buiting K (2010) Prader-Willi syndrome and Angelman syndrome. Am J Med Genet C: Semin Med Genet 154C:365–376. doi:10.1002/ajmg.c.30273
13. Butler MG, Smith BK, Lee J, Gibson C, Schmoll C, Moore WV, Donnelly JE (2013) Effects of growth hormone treatment in adults with Prader-Willi syndrome. Growth hormone & IGF research : official journal of the Growth Hormone Research Society and the International IGF Research Society 23:81–87. doi:10.1016/j.ghir.2013.01.001
14. Clarke D (1998) Prader-Willi syndrome and psychotic symptoms: 2. A preliminary study of prevalence using the Psychopathology Assessment Schedule for Adults with Developmental Disability checklist. J Intellect Disabil Res 42(Pt 6):451–454
15. Deb S, Unwin G, Deb T (2014) Characteristics and the trajectory of psychotropic medication use in general and antipsychotics in particular among adults with an intellectual disability who exhibit aggressive behaviour. J Intellect Disabil Res. doi:10.1111/jir.12119
16. Dech B, Budow L (1991) The use of fluoxetine in an adolescent with Prader-Willi syndrome. J Am Acad Child Adolesc Psychiatry 30:298–302. doi:10.1097/00004583-199103000-00020
17. Dolengevich Segal H, Rodriguez Salgado B, Conejo Garcia A, San Sebastian Cabases J (2006) Efficacy of topiramate in children and adolescent with problems in impulse control: preliminary results. Actas Esp Psiquiatr 34:280–282
18. Duggan L, Brylewski J (1999) Effectiveness of antipsychotic medication in people with intellectual disability and schizophrenia: a systematic review. J Intellect Disabil Res 43(Pt 2):94–104

19. Durst R, Rubin-Jabotinsky K, Raskin S, Katz G, Zislin J (2000) Risperidone in Prader-Willi syndrome. J Am Acad Child Adolesc Psychiatry 39:545–546. doi:10.1097/00004583-200005000-00004
20. Durst R, Rubin-Jabotinsky K, Raskin S, Katz G, Zislin J (2000) Risperidone in treating behavioural disturbances of Prader-Willi syndrome. Acta Psychiatr Scand 102:461–465
21. Dykens EM, Roof E (2008) Behavior in Prader-Willi syndrome: relationship to genetic subtypes and age. J Child Psychol Psychiatry 49:1001–1008
22. Fieldstone A, Zipf WB, Sarter MF, Berntson GG (1998) Food intake in Prader-Willi syndrome and controls with obesity after administration of a benzodiazepine receptor agonist. Obes Res 6:29–33
23. Francey SM, Nelson B, Thompson A, Parker AG, Kerr M, Macneil C, Fraser R, Hughes F, Crisp K, Harrigan S, Wood SJ, Berk M, McGorry PD (2010) Who needs antipsychotic medication in the earliest stages of psychosis? A reconsideration of benefits, risks, neurobiology and ethics in the era of early intervention. Schizophr Res 119:1–10
24. Goldstone AP, Holland AJ, Hauffa BP, Hokken-Koelega AC, Tauber M, speakers contributors at the Second Expert Meeting of the Comprehensive Care of Patients with PWS (2008) Recommendations for the diagnosis and management of Prader-Willi syndrome. J Clin Endocrinol Metab 93:4183–4197. doi:10.1210/jc.2008-0649
25. Hassler F, Reis O (2010) Pharmacotherapy of disruptive behavior in mentally retarded subjects: a review of the current literature. Dev Disabil Res Rev 16:265–272. doi:10.1002/ddrr.119
26. Herguner S, Mukaddes NM (2007) Psychosis associated with fluoxetine in Prader-Willi syndrome. J Am Acad Child Adolesc Psychiatry 46:944–945. doi:10.1097/chi.0b013e318068fbed
27. Itoh M, Koeda T, Ohno K, Takeshita K (1995) Effects of mazindol in two patients with Prader-Willi syndrome. Pediatr Neurol 13:349–351
28. Jauregi J, Arias C, Vegas O, Alen F, Martinez S, Copet P, Thuilleaux D (2007) A neuropsychological assessment of frontal cognitive functions in Prader-Willi syndrome. J Intellect Disabil Res 51:350–365
29. Kennedy GM, Lhatoo SD (2008) CNS adverse events associated with antiepileptic drugs. CNS Drugs 22:739–760
30. Khan A, Faught E, Gilliam F, Kuzniecky R (1999) Acute psychotic symptoms induced by topiramate. Seizure 8:235–237
31. Kohn Y, Weizman A, Apter A (2001) Aggravation of food-related behavior in an adolescent with Prader-Willi syndrome treated with fluvoxamine and fluoxetine. Int J Eat Disord 30:113–117
32. Kyriakides M, Silverstone T, Jeffcoate W, Laurance B (1980) Effect of naloxone on hyperphagia in Prader-Willi syndrome. Lancet 1:876–877
33. Lee YJ, Marcu S, Berall G, Shapiro CM (2011) Tryptophan for the treatment of excessive daytime sleepiness in Prader-Willi syndrome. Indian Pediatr 48:319–321
34. Lin G, Lawrence R (2006) Pediatric case report of topiramate toxicity. Clin Toxicol (Phila) 44:67–69
35. Matthews SC, Miller BP (2001) Auditory hallucinations associated with topiramate. J Clin Psychiatry 62:653
36. Miller JL, Angulo M (2014) An open-label pilot study of N-acetylcysteine for skin-picking in Prader-Willi syndrome. Am J Med Genet A 164:421–424. doi:10.1002/ajmg.a.36306
37. Morgan JR, Storch EA, Woods DW, Bodzin D, Lewin AB, Murphy TK (2010) A preliminary analysis of the phenomenology of skin-picking in Prader-Willi syndrome. Child Psychiatry Hum Dev 41:448–463. doi:10.1007/s10578-010-0180-7
38. Motaghedi R, Lipman EG, Hogg JE, Christos PJ, Vogiatzi MG, Angulo MA (2011) Psychiatric adverse effects of rimonobant in adults with Prader Willi syndrome. Eur J Med Genet 54:14–18. doi:10.1016/j.ejmg.2010.09.015
39. Mula M, Trimble MR, Lhatoo SD, Sander JW (2003) Topiramate and psychiatric adverse events in patients with epilepsy. Epilepsia 44:659–663
40. Orphanet (2013) Prevalence of rare diseases. http://www.orpha.net/orphacom/cahiers/docs/FR/Prevalence_des_maladies_rares_par_prevalence_decroissante_ou_cas.pdf. Accessed January 2014
41. Rana F, Gormez A, Varghese S (2013) Pharmacological interventions for self-injurious behaviour in adults with intellectual disabilities. The Cochrane database of systematic reviews 4:CD009084. doi:10.1002/14651858.CD009084.pub2
42. Reas DL, Grilo CM (2008) Review and meta-analysis of pharmacotherapy for binge-eating disorder. Obesity (Silver Spring) 16:2024–2038
43. Reis AD, Castro LA, Faria R, Laranjeira R (2008) Craving decrease with topiramate in outpatient treatment for cocaine dependence: an open label trial. Rev Bras Psiquiatr 30:132–135
44. Schepis C, Failla P, Siragusa M, Palazzo R, Romano C (1998) Failure of fluoxetine to modify the skin-picking behaviour of Prader-Willi syndrome. Australas J Dermatol 39:57–58
45. Selikowitz M, Sunman J, Pendergast A, Wright S (1990) Fenfluramine in Prader-Willi syndrome: a double blind, placebo controlled trial. Arch Dis Child 65:112–114
46. Semenza C, Pignatti R, Bertella L, Ceriani F, Mori I, Molinari E, Giardino D, Malvestiti F, Grugni G (2008) Genetics and mathematics: evidence from Prader-Willi syndrome. Neuropsychologia 46:206–212
47. Shapira NA, Lessig MC, Lewis MH, Goodman WK, Driscoll DJ (2004) Effects of topiramate in adults with Prader-Willi syndrome. American journal of mental retardation : AJMR 109:301–309. doi:10.1352/0895-8017(2004)109<301:EOTIAW>2.0.CO;2
48. Shapira NA, Lessig MC, Murphy TK, Driscoll DJ, Goodman WK (2002) Topiramate attenuates self-injurious behaviour in Prader-Willi Syndrome. The international journal of neuropsychopharmacology / official scientific journal of the Collegium Internationale Neuropsychopharmacologicum 5:141–145. doi:10.1017/S1461145702002833
49. Sinnema M, Boer H, Collin P, Maaskant MA, van Roozendaal KE, Schrander-Stumpel CT, Curfs LM (2011) Psychiatric illness in a cohort of adults with Prader-Willi syndrome. Res Dev Disabil 32:1729–1735. doi:10.1016/j.ridd.2011.02.027
50. Skokauskas N, Sweeny E, Meehan J, Gallagher L (2012) Mental health problems in children with prader-willi syndrome. Journal of the Canadian Academy of Child and Adolescent Psychiatry = Journal de l'Academie canadienne de psychiatrie de l'enfant et de l'adolescent 21:194–203
51. Smathers SA, Wilson JG, Nigro MA (2003) Topiramate effectiveness in Prader-Willi syndrome. Pediatr Neurol 28:130–133
52. Soni S, Whittington J, Holland AJ, Webb T, Maina E, Boer H, Clarke D (2007) The course and outcome of psychiatric illness in people with Prader-Willi syndrome: implications for management and treatment. J Intellect Disabil Res 51:32–42. doi:10.1111/j.1365-2788.2006.00895.x
53. Soni S, Whittington J, Holland AJ, Webb T, Maina EN, Boer H, Clarke D (2008) The phenomenology and diagnosis of psychiatric illness in people with Prader-Willi syndrome. Psychol Med 38:1505–1514
54. Stella F, Caetano D, Cendes F, Guerreiro CA (2002) Acute psychotic disorders induced by topiramate: report of two cases. Arq Neuropsiquiatr 60:285–287
55. Unwin GL, Deb S (2011) Efficacy of atypical antipsychotic medication in the management of behaviour problems in children with intellectual disabilities and borderline intelligence: a systematic review. Res Dev Disabil 32:2121–2133. doi:10.1016/j.ridd.2011.07.031
56. Van Borsel J, Defloor T, Curfs LM (2007) Expressive language in persons with Prader-Willi syndrome. Genet Couns 18:17–28

57. Vogels A, Matthijs G, Legius E, Devriendt K, Fryns JP (2003) Chromosome 15 maternal uniparental disomy and psychosis in Prader-Willi syndrome. J Med Genet 40:72–73
58. Whitman BY, Accardo P (1987) Emotional symptoms in Prader-Willi syndrome adolescents. Am J Med Genet 28:897–905
59. Whittington J, Holland A, Webb T, Butler J, Clarke D, Boer H (2004) Academic underachievement by people with Prader-Willi syndrome. J Intellect Disabil Res 48: 188–200
60. Wu K, Hanna GL, Easter P, Kennedy JL, Rosenberg DR, Arnold PD (2013) Glutamate system genes and brain volume alterations in pediatric obsessive-compulsive disorder: a preliminary study. Psychiatry Res 211:214–220. doi:10.1016/j.pscychresns.2012.07.003