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REVIEW

Treatment Options for Psychotic Depression in Adolescents: A Comprehensive Review

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Abstract: Despite being associated with increased illness severity and suicidality compared to non-psychotic depression, psychotic depression remains under-researched, particularly in adolescents. With this article, we aim to review treatment options for psychotic depression in adolescents. We performed a multi-step narrative review, first identifying studies on adolescents with psychotic depression evaluating any intervention and with any methodological design. We subsequently complemented our search with systematic reviews and meta-analysis evaluating treatment interventions in adults with psychotic depression and adolescents with bipolar depression. Finally, we reviewed clinical guidelines to complement the evidence found and provided recommendations for clinical practice. Based on the findings, we recommend a stepped approach to the treatment of psychotic depression in adolescents. For mild cases with predominance of depressive symptoms, antidepressant monotherapy with a serotonin selective reuptake inhibitor (eg fluoxetine, sertraline or citalopram) could be trialed first. In severe presentations, antidepressant-antipsychotic combination would be the treatment of choice. The antidepressant-antipsychotic combination has been recommended by several clinical guidelines, systematic reviews and meta-analysis in this population, adolescents with bipolar depression and adults with psychotic depression. Another combination of antidepressant-antipsychotic with evidence from a case report is the fluoxetine-quetiapine combination. For those adolescents not responding to the antidepressant-antipsychotic combination, or those requiring a rapid response or unable to take medication, electroconvulsive therapy could be considered. Psychological interventions (eg cognitive behavioral therapy, family therapy or interpersonal psychotherapy training for adolescents) are recommended by clinical guidelines but require further research. Overall, literature on the field is scarce and limited, with most evidence coming from adults and other populations. Further research into effective and safe treatment of psychotic depression in adolescent population is needed.

Keywords: treatment, psychosis, mood, teenager

Introduction

Psychotic depression is a clinical presentation characterized by a combination of depressive symptoms as low mood, apathy and anhedonia, and psychotic symptoms as hallucinatory or delusional experiences.[1] Psychotic depression was initially classified by Emil Kraepelin as a subtype of 'manic-depressive illness'.[2] In post-Kraepelinian times, psychotic depression has been included as a separate subtype of unipolar depressive disorder in the two main diagnostic classification manuals: The International Classification of Diseases (ICD) and the Diagnostic and statistical manual of mental disorders (DSM).[1,3] Initially conceptualized as a severe presentation of unipolar depressive disorder, the most recent editions of DSM and ICD allow to diagnose psychotic depression in less severe presentations, acknowledging that the severity of mood symptoms is not necessarily a requirement for an individual to present with psychotic features.[4]

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Psychotic depression is defined under the current diagnostic manuals as "Single Episode (or Recurrent) Depressive Disorder, Moderate or Severe, with psychotic symptoms" in the ICD-11;[1] and as "Major Depressive Disorder with psychotic features" in the DSM-5[3] (see Table 1 for ICD-11 and DSM-5 criteria).

Psychotic depression has an estimated lifetime prevalence of 0.35–1%.[5] It has been associated with increased illness severity, more severe functional impairment and longer episode duration than non-psychotic depression, as well as with a risk of recurrence of psychotic features in subsequent depressive episodes.[6] Psychotic depression is also linked with higher risk of suicidality.[7]

Despite its clinical relevance, psychotic depression is worryingly often missed and underdiagnosed in clinical practice,[8] particularly among adolescents. This condition remains remarkably under-researched compared to other mental health diagnoses, such as schizophrenia.[9] The research gap is even more pronounced when it comes to the child and adolescent population, with far fewer studies focusing on these age group compared to adults.[10]

With this work, we aim to carry out a comprehensive review of the available literature in order to make recommendations on treatment options available for adolescents with psychotic depression. Identification and effective treatment in this condition is key. However, from a treatment perspective, very little is known about available treatment options for psychotic depression in adolescence. This lack of knowledge is reflected in guidelines, which provide limited recommendations. For instance, the National Institute for Health and Care Excellence (NICE) recommends considering augmenting antidepressant treatment with a second-generation antipsychotic but does not specify which particular drugs should be used.[11]

Table 1 ICD-11 and DSM-5 Diagnostic Criteria for Psychotic Depression

	ICD-11[1]	DSM-5[3]
Nomenclature	6A70.2 Single episode depressive disorder, moderate, with psychotic symptoms 6A70.4 Single episode depressive disorder, severe, with psychotic symptoms	296.24 Major depressive disorder, single episode with (mood-congruent/mood-incongruent) psychotic features
Mood	Depressed mood or diminished interest in activities	Depressed mood (In children and adolescents, can be irritable mood).
Frequency/ duration	Most of the day, nearly every day during a period lasting at least two weeks	Most of the day, nearly every day, as indicated by either subjective report or observation made by others. Two-week period.
Accompanying symptoms	- Difficulty concentrating - Feelings of worthlessness or excessive or inappropriate guilt - Hopelessness - Recurrent thoughts of death or suicide - Changes in appetite or sleep - Psychomotor agitation or retardation - Reduced energy or fatigue	- Diminished interest or pleasure in all, or almost all, activities - Significant weight loss or weight gain or decrease or increase in appetite. (In children, consider failure to make expected weight gain). - Insomnia or hypersomnia - Psychomotor agitation or retardation - Fatigue or loss of energy - Feelings of worthlessness or excessive or inappropriate guilt - Diminished ability to think or concentrate or indecisiveness - Recurrent thoughts of death, recurrent suicidal ideation, a suicide attempt or a specific plan for committing suicide
Psychotic symptoms	Presence of delusions or hallucinations during the depressive episode	Delusions and/or hallucinations are present. - Mood-congruent: The content of all delusions and hallucinations is consistent with themes of personal inadequacy, guilt, disease, death, nihilism, or deserved punishment. - Mood-incongruent: The content of the delusions or hallucinations does not involve themes described above, or the content is a mixture of mood-incongruent and mood-congruent themes.

Abbreviations: ICD,: International Classification of Diseases; DSM, Diagnostic and statistical manual of mental disorders.

Previous reviews have looked at associations between psychotic depression and poor outcomes. For instance, a review found a correlation between psychotic experiences and depression in early teenage years and poorer educational, occupational and social outcomes later in life.[12] Other recent reviews have evaluated the treatment options of psychotic depression.[13] However, they did not include studies with participants under the age of 18 years.

Through a narrative evidence-based review, we aimed to evaluate the efficacy of pharmacological and non-pharmacological Interventions for psychotic depression in adolescents. To the best of our knowledge, this is the first study evaluating the available evidence on the efficacy and safety of pharmacological and non-pharmacological interventions for adolescents with psychotic depression. We also provided treatment recommendations based on that evidence.

Materials and Methods

We performed a multi-step narrative review in order to provide evidence-based recommendations. The full process and results are summarized in Figure 1. We aimed to evaluate comprehensively the evidence of pharmacological and non-pharmacological interventions in adolescents with psychotic depression.

Since this was our primary goal, we first identified studies evaluating a) adolescents (defined as individuals between the ages of 12 and 19, including samples with mean age <18 years only), b) with a diagnosis of unipolar major depressive disorder with psychotic features as defined by the ICD or DSM criteria (any version[1,3,14–17]), c) evaluating any pharmacological and non-pharmacological intervention, d) with any methodological design including case series and clinical cases but excluding protocols. The decision to include case series was due to the scarcity of research literature available found.

In a second step, and in the context of to the scarcity of research literature available in our population of interest, we complemented our search with systematic reviews and meta-analyses, as well as a network meta-analyses, evaluating pharmacological and non-pharmacological interventions in adults with (unipolar) psychotic depression and adolescents with bipolar depression (BD). We note the limitations related to the age for the first (note adolescents are not small adults[18]) and diagnostic construct for the latest (adolescents with BD may present with manic/depressive symptoms

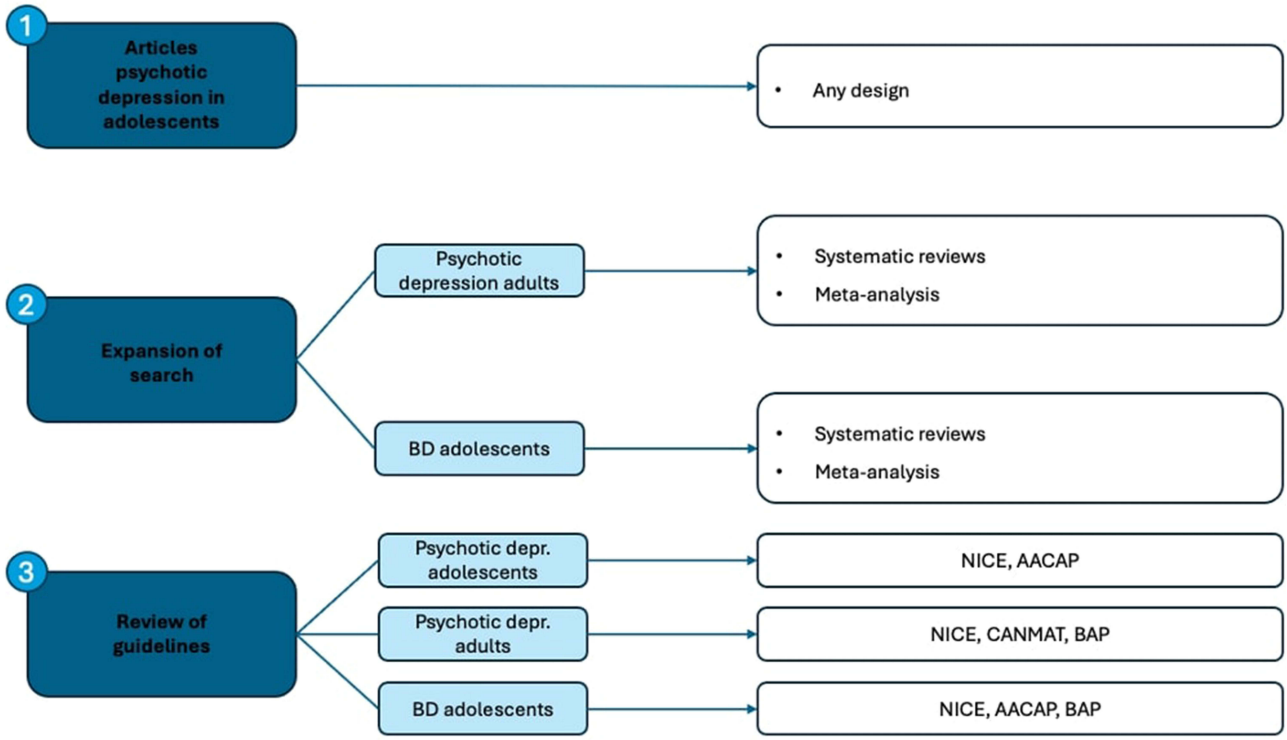

Figure 1 Multi-step narrative review. **Abbreviations**: BD, bipolar depression; Depr., depression; NICE, National Institute for Health and Care Excellence; AACAP, American Academy of Child and Adolescent Psychiatry; CANMAT, Canadian Network for Mood and Anxiety Treatments; BAP, British Association for Psychopharmacology.

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without psychotic features). However, extrapolating data from adults is acceptable according to several guidelines[19,20] when not enough specific evidence is available on adolescents. For studies on the treatment of psychotic depression in adults, we present the evidence on systematic reviews and meta-analysis (as the studies with the highest level of evidence), conducted on adults with a diagnosis of psychotic depression defined by ICD or DSM criteria. Their respective nomenclatures are described in Table 1. For the studies on interventions for adolescents with BD, we present the evidence on systematic reviews and meta-analysis and a network meta-analysis, conducted on adolescents.

Third, we present the recommendations provided by clinical guidelines to complement the evidence found. For the treatment of psychotic depression in adolescents, we included recommendations from the NICE guidelines and guidelines issued by the American Academy of Child and Adolescent Psychiatry (AACAP). For the treatment of psychotic depression in adults, we consulted the NICE guidelines, the Canadian Network for Mood and Anxiety Treatments (CANMAT) and the British Association for Psychopharmacology (BAP). Lastly, for the treatment of BD in adolescents, we gathered recommendations from NICE, AACAP and BAP guidelines.

Results

Efficacy and Safety of Pharmacological and Non-Pharmacological Interventions for Adolescents with Psychotic Depression

We found 8 studies assessing interventions for adolescents with psychotic depression: 2 retrospective reviews of medical records of young people receiving electroconvulsive therapy (ECT);[21,22] a case series reporting on antidepressant-antipsychotic combination;[23] another case series reporting on ECT;[24] and 3 case reports reporting on the therapeutic use of ketamine,[25] sertraline[26] and the fluoxetine-quetiapine combination,[27] respectively.

The first retrospective review included 13 adolescents with psychotic depression who underwent ECT treatment due to not responding to medication or presenting with severe adverse reactions to medication (such as neuroleptic malignant syndrome). 100% of individuals presented with a marked improvement or resolution of affective symptoms and 83% with a marked improvement or resolution of psychotic symptoms. No severe adverse effects were reported.[21] The second retrospective review gathered medical records of 10 patients aged 13–19 with a diagnosis of psychotic depression receiving ECT after non-response to pharmacological treatment or presence of severe symptoms requiring a quick response (catatonia, poor nutrition, repeated suicidal attempts). 100% of the individuals showed improvement of symptoms. Of note, 3 young people developed a rapid cycling bipolar disorder during follow-up, two of whom presented with a treatment-emergent manic affective switch during ECT treatment.[22]

Evidence obtained from case reports and case series is summarized in Table 2. Briefly, the antidepressant-antipsychotic combination was effective in two case reports (using fluoxetine-quetiapine and amitriptyline-thioridazine, respectively)[27,28] and a case series using desipramine with trifluoperazine/chlorpromazine.[23] Antidepressant monotherapy (sertraline) was also effective in a case report, leading to a quick improvement of psychotic symptoms after a month and remission of depressive symptoms after 4 months.[26] For individuals with psychotic depression not responding to pharmacological intervention, a case report published the use of ketamine[25] and two case series reported on the use of ECT[24,29] with positive results.

Efficacy and Safety of Pharmacological and Non-Pharmacological Interventions for Adults with Psychotic Depression

Five systematic reviews and meta-analysis reported on this topic, four of them investigating the efficacy of any pharmacological intervention for psychotic depression in adults[30–33] and one comparing the antidepressant-antipsychotic combination to monotherapy of either of those drugs.[34]

The first systematic review and meta-analysis found that ECT was more effective than tricyclic antidepressants (TCA) ($p<0.05$) for the treatment of psychotic depression in adults but did not find statistically significant differences between ECT and the TCA-first-generation antipsychotic combination or ECT and first-generation antipsychotic monotherapy.[33]

The second systematic review and meta-analysis found that the antidepressant-antipsychotic combination was more efficacious than antipsychotic monotherapy for depressive symptoms in adults with psychotic depression (ES=0.49, CI:

Table 2 Summary of Case Reports and Case Series of Adolescents with Psychotic Depression

First Author, Year	DESIGN: SAMPLE SIZE	DEMOGRAPHICS	DIAGNOSIS	TREATMENT	OUTCOME	ADVERSE EFFECTS
Liu, 2024[26]	Case report: 1	17 yo female	Psychotic depression and dystonia	Sertraline	-Significant improvement of mood, aggression and psychotic symptoms, as well as overall functionality -Only partial improvement of dystonia	-Daytime sleepiness
Padla, 2001[27]	Case report: 1	15 yo male	Psychotic depression	Quetiapine + fluoxetine	Remission of mood and psychotic symptoms	Not mentioned
Salmon, 2001[28]	Case report: 1	13 yo male	Psychotic depression and separation anxiety	Amitriptyline + thioridazine	Remission and improvement of functionality More detail into specific symptom improvement not provided	Not mentioned
Zarrinnegar, 2019[25]	Case report: 1	15 yo, sex not specified	Psychotic depression, PTSD, GAD, suicide attempt through OD	Ketamine infusion	Improvement in mood and suicidal ideation	Derealization and nausea
Conrad, 1986[23]	Case series: 2	Female adolescents (age not specified)	Psychotic depression	Desipramine + antipsychotic	-Psychotic and depressive symptoms improved but worsened when levels of desipramine rose, symptoms improved again when levels were reduced to below 200ng/mL	Worsening of symptoms with higher levels of desipramine
Ghaziuddin, 1996[24]	Case series: 2	15 and 16 yo, sex not specified	Treatment-resistant psychotic depression	ECT	- Significant improvement of depression in one -Significant improvement of functionality in both	-Cognitive worsening (attention, verbal delayed retention, long-term memory search) -Headaches (80% total) -Nausea/vomiting (64% total) -Tardive seizures (10% total) -Prolonged seizures (9.6% total)

(*Continued*)

Table 2 (Continued).

First Author, Year	DESIGN: SAMPLE SIZE	DEMOGRAPHICS	DIAGNOSIS	TREATMENT	OUTCOME	ADVERSE EFFECTS
Warren, 1989[29]	Case series: 1	17 yo female	Down's syndrome and psychotic depression, not responding to one course of antidepressants	ECT	Recuperated functionality, no description of symptoms improvement	Not mentioned

Abbreviations: ECT, Electroconvulsive therapy; GAD, generalized anxiety disorder; n.a, not available; PTSD, post-traumatic stress disorder.

0.23, 0.75), but only trended superiority in improving psychotic symptoms (p=0.06). The antidepressant-antipsychotic combination also trended superiority compared to antidepressant monotherapy in improving depressive symptoms (p=0.09), but not psychotic symptoms. All-cause-discontinuation and reported side effect rates were similar in all pharmacological treatments and placebo, except for more somnolence with antipsychotic-antidepressant co-treatment versus antidepressants (RR=2.79, CI: 1.14, 6.79).[34]

Three Cochrane Guidelines have been published on the pharmacological treatment of psychotic depression in adults. The first one published in 2005 found that the antidepressant-antipsychotic combination was more effective than antipsychotic alone (RR=1.92, CI: 1.32, 2.80), but not than antidepressant monotherapy (RR=1.44, CI: 0.86, 2.41) in the treatment of depressive symptoms in adults with psychotic depression. There were no statistically significant differences in the overall drop-out rates between any of the treatments.[30] Authors updated this systematic review in 2013 including new literature (2 further randomized clinical trials) and found evidence that the antidepressant-antipsychotic combination was more effective than antidepressant monotherapy (RR=1.49, CI: 1.12, 1.98), antipsychotic monotherapy (RR=1.83, CI: 1.40, 2.38) and placebo (RR=1.86, CI: 1.23, 2.82) for the treatment of depressive symptoms in adults with psychotic depression.[31] The most recent version of this work, published in 2021, found that the antidepressant-antipsychotic combination was more effective than antipsychotic monotherapy (RR=1.83, CI: 1.40, 2.38), antidepressant monotherapy (RR=1.42, CI: 1.11, 1.80), and placebo (RR=1.86, CI: 1.23, 2.82) for the treatment of depressive symptoms in adults with psychotic depression. No difference in overall dropouts between the combination of the antidepressant-antipsychotic combination versus antipsychotic monotherapy (RR=0.79, CI: 0.63, 1.01), antidepressant monotherapy (RR=0.91, CI: 0.55, 1.50), or placebo alone (RR=0.75, CI: 0.48, 1.18)[32] was found. To note, bias related to heterogeneity in the studies included was highlighted.

Efficacy and Safety of Pharmacological and Non-Pharmacological Interventions for Adolescents with BD

We found two pair-wise meta-analyses[35,36] and a network meta-analysis[37] evaluating the efficacy of lurasidone, quetiapine and the olanzapine-fluoxetine combination (OFC) in the acute treatment of BD in adolescents, and two systematic reviews[38,39] compared the efficacy of quetiapine with placebo.

None of the two systematic reviews comparing quetiapine to placebo[38,39] found quetiapine to be more efficacious for the acute treatment of BD in adolescents. Further, although no differences were found in discontinuation rates of quetiapine versus placebo, one of the meta-analyses linked quetiapine to significantly higher weight gain and increase in triglyceride levels than placebo.[39]

A network meta-analysis[37] found that both lurasidone and OFC were more efficacious than placebo in improving depressive symptoms in adolescents with BD (lurasidone: −5.70, CI: −8.66, −2.76; OFC: −5.0, CI: −8.63, −1.38), but

quetiapine was not. Lurasidone was linked to less weight gain and smaller impacts on cholesterol and triglycerides compared with quetiapine and OFC.

A pair-wise meta-analysis[35] found that lurasidone had a significantly higher response in improving depressive symptoms in adolescents with BD, compared with placebo (59.5% vs 36.5%; p<0.001; Mean Difference=−5.70, CI: −8.67, −2.73). OFC was also found to have significantly higher rates of response when compared to placebo (78.2% vs 59.2%, p=0.003; Mean Difference=−5.00, CI: −8.64, −1.36). Lurasidone had significantly higher risk of nausea, somnolence and weight gain than placebo. It was also linked to an increase in cholesterol levels. OFC was linked to weight gain, increased appetite and elevated triglycerides. Quetiapine was linked to headaches, sedation and dizziness, as well as an increase in triglycerides and thyroid-stimulating hormone (TSH) levels.

Finally, another pair-wise meta-analysis[36] concluded that quetiapine was not more efficacious than placebo to treat depressive symptoms in adolescents with BD, whilst OFC produced statistically significant improvements (Mean Difference=−5.00, CI: −8.64, −1.36) and lurasidone too (Mean Difference=−5.7, CI: −8.66, −2.74). None of the drugs presented with higher rates of discontinuation due to side effects when compared to placebo (all p>0.05). When pooling together all the studies comparing remission rates to antipsychotics (excluding OFC) versus placebo, antipsychotics presented with higher rates of remission (RR=1.35, CI: 1.11, 1.63).

Recommendations Provided by Clinical Guidelines

For adolescents with psychotic depression, The AACAP Practice Parameter for the Assessment and Treatment of Children and Adolescents With Depressive Disorders (2007),[40] states that "mild or vague" psychotic symptoms in a depressed child might respond to antidepressant monotherapy. It also highlights that clinical consensus recommends the combination of selective serotonin reuptake inhibitors (SSRIs) and atypical antipsychotics as the treatment of choice for psychotic depression. NICE guidelines (2019)[11] recommend intensive psychological therapy (cognitive behavioral therapy, interpersonal training for adolescents or family therapy) with or without an antidepressant (namely fluoxetine, sertraline or citalopram), and to consider augmenting the antidepressant with a second-generation antipsychotic. Both guidelines report that the duration of antipsychotic treatment is unknown, with AACAP recommending aiming for antidepressant monotherapy once psychotic symptoms remit.

For adults with psychotic depression, NICE guidelines (2022)[41] recommend an antidepressant-antipsychotic combination (such as quetiapine or olanzapine), or antidepressant monotherapy if the patient prefers. They also support the addition of psychological treatment when acute symptoms improve. BAP guidelines (2015)[42] recommend the combination of antidepressants and antipsychotics over antidepressant or antipsychotic monotherapy (level of evidence A). They also stated that ECT could be the treatment of choice in severe cases where a quick response is needed, flagging that relapse rates post-ECT are high. Lastly, CANMAT[43] guidelines suggest the antidepressant-antipsychotic combination as the first line of treatment for psychotic depression (level of evidence 1).

For adolescents with BD, NICE guidelines (2023)[19] recommend a psychological intervention for at least three months and follow recommendations for adult population adjusting them to the British National Formulary for Children (BNFC). First line of treatment would be OFC, or quetiapine monotherapy. Olanzapine or lamotrigine monotherapy can also be considered if the individual prefers. NICE advice not to routinely maintain antipsychotic treatment for longer than 12 weeks unless clinically indicated. The AACAP Practice Parameter (2007)[44] recommends to begin treatment with an agent approved for the treatment of bipolar disorder in adults, such as OFC. Antidepressants can also be prescribed if the young person is already taking a mood stabilizer. ECT is only recommended for the treatment of bipolar disorder type I and severe episodes not responding to (or unable to tolerate or comply with) medication. AACAP also highlight that child and adolescent (C&A) population is likely to need other interventions alongside pharmacological therapy.

BAP (2016)[20] recommend extrapolating data from recommendations for adult population, which indicate lamotrigine, usually in combination with antimanic agents, as the option with best available evidence (GRADE 4), followed by quetiapine, lurasidone and olanzapine or OFC (all GRADE 3). ECT is recommended in cases of high severity, such as those with psychotic symptoms or high suicide risk, and cases not responding to medication (GRADE 3). BAP note that antidepressants may induce manic affective switches more often in child and adolescent population when compared to adults.

Discussion

To our knowledge, this is the first review evaluating available treatment options for adolescents with psychotic depression. Direct evidence for the treatment of this condition in adolescents is scarce and was obtained from non-controlled studies and case reports/case series. By extrapolating findings from the treatment of BD in adolescent and psychotic depression in adults, we complemented this evidence to provide evidence-based recommendations. In line with this, the first key message is that the evidence from this population is very limited, and more studies are needed, particularly regarding psychological interventions, which are recommended by clinical guidelines for this population.

The second key message and recommendation are that the antidepressant-antipsychotic combination should be used in severe cases. This is supported by case reports and series of its use in adolescent population with psychotic depression[23,27,28] as well as evidence from meta-analysis on its effectiveness over antidepressant or antipsychotic monotherapy in adults with psychotic depression[30–34] and adolescents with BD.[35–37] The antidepressant-antipsychotic combination has also shown to be more effective than monotherapy of either drug or placebo in the latest versions of the Cochrane systematic review.[31,32]

Specific combinations reported in the literature are quetiapine-fluoxetine (with the limitation that it was used in a case report of an adolescent with psychotic depression)[27] and OFC (with evidence widely supported by literature on the treatment of BD in adolescents – but not psychotic depression).[35–37] OFC was also found to be the treatment with best evidence available in a recent network meta-analysis conducted on the treatment of psychotic depression in adults,[13] which was not included in our review due to including adults with BD and not only unipolar psychotic depression. Other case reports and a case series used the combination of antipsychotic-TCA (thioridazine-amitriptyline, trifluoperazine-desipramine and chlorpromazine-desipramine),[23,28] which were also used in some of the randomized clinical trials included in the Cochrane systematic reviews.[30–32] However, we do not recommend this combination given the lack of robust evidence of its efficacy of TCA in the treatment of depression in C&A population.[45] It is also worth noting that first generation antipsychotics have been linked to higher rates of discontinuation in early onset psychosis compared to second generation antipsychotics.[46] Of note, some second-generation antipsychotics like quetiapine and olanzapine have been associated with significant cardiometabolic side effects in C&A.[47,48] Monitoring requirements are outlined by NICE in their clinical guideline on management of psychosis and schizophrenia in C&A and include regular monitoring of cardiometabolic risk factors.[49] Other antipsychotics with lower risk of discontinuation and more favorable side effect profile could be considered,[47] such as aripiprazole, lurasidone[46] (noting there have been reports of treatment-emergent affective switch[50–52]), ziprasidone or molindone, if available.[47] Further research on their efficacy in treating psychotic depression in adolescents is needed.

In mild to moderate cases, treatment with antidepressant monotherapy could result in the improvement of psychotic symptoms.[26,40] However, it is worth noting that antidepressants are linked to higher risk of treatment-emergent affective switch in C&A population[20] and antipsychotics can reduce this risk.

Interestingly, ECT seems to be the most studied intervention in adolescents with psychotic depression, typically used in resistant cases. The evidence available, however, was found in non-controlled studies[21,22] and case series.[24,29] Pharmacological treatment was maintained in some studies[21,22] during the course of ECT treatment, making it difficult to ascertain the effect of ECT as an independent treatment. Further, several of the side effects reported such as memory loss and nausea caused significant discomfort to individuals having received ECT treatment even when they did not lead to discontinuation of the ECT course.[22] Of note, there were some reports of treatment-emergent manic affective switch during the course of ECT, a risk to be considered.[22] Taking this into account, our recommendation is to use ECT only in cases not responding to pharmacological medication, unable to take medication or in which symptom severity or suicidal ideation needs a quick response. This indication aligns with recommendations made in several of the clinical guidelines reviewed.[20,42,44] Another intervention to be considered in adolescents with treatment-resistant psychotic depression with predominance of psychotic symptoms would be clozapine, which has shown efficacy in treatment-resistant early-onset psychosis[46] and improvement of negative symptoms in such cases.[53] Given its efficacy in treatment-resistant depression in adult population[54,55] and some reports of efficacy in adolescents with treatment-resistant depression,[25] ketamine could

be another option in treatment-resistant cases. However, it is worth noting again that the studies in the literature have been conducted in early-onset schizophrenia, warranting more studies in this specific population.

In summary, and taking into consideration the evidence found, we support a stepped approach in the treatment of psychotic depression in adolescents. For mild cases with predominance of depressive symptoms over psychotic features, antidepressant monotherapy with an SSRI such as fluoxetine, sertraline or citalopram could be trialed as the first line. If not responding to monotherapy or in more severe presentations with predominance of psychotic features, the antidepressant-antipsychotic combination would be the treatment of choice. OFC is our main recommendation, having been recommended in numerous clinical guidelines for C&A with BD[19,20,24] as well as systematic reviews and meta-analysis in this population.[35–37] Although not explicitly mentioned as a combination, NICE guidelines for psychotic depression in C&A and AACAP recommend combining an SSRI with an atypical antipsychotic[11,40] and NICE guidelines for psychotic depression in adults[41] and a recent network meta-analysis[13] also recommend combining an antipsychotic such as olanzapine with an antidepressant, with the network meta-analysis being explicit in recommending OFC. For treatment-resistant cases not responding to the antidepressant-antipsychotic combination, and severe cases needing a rapid response to treatment or unable to take medication, ECT should be considered.

Lastly, psychological interventions have shown promising results in the treatment of BD in adolescents,[56] including family-focused therapy (FFT), which reduced the duration of depressive symptoms when in combination with treatment as usual (pharmacotherapy with mood stabilizers, antipsychotics and adjuvant antidepressants)[57] and child and family-focused cognitive-behavioral therapy (CFF-CBT), which was associated with an improvement in mood symptoms and functionality compared to treatment as usual.[58] Given these findings and taking into account guideline recommendations to consider psychological interventions for adolescents with psychotic depression, further research into psychological interventions for this specific population is needed.

The importance of differential diagnosis in the choice of treatment must also be highlighted. Brief psychotic symptoms and brief hallucinations (nondiagnostic phenomena) are common in child and adolescent population, and specific literature on the treatment of clinical high-risk presentations can guide decision making on when to introduce antipsychotic medication and psychological treatment.[59]

Linked to this, the clinical high-risk of psychosis (CHR-P) paradigm is crucial in adolescence, as it allows early detection of adolescents who have higher probability of developing a psychotic disorder.[60] Within CHR-P population, attenuated psychotic symptoms are often accompanied by comorbid mental disorders, with 41% of individuals presenting with a depressive disorder.[61] As such, many PD presentations could be better framed within the CHR-P paradigm. On the other hand, depressive symptoms are also prevalent amongst CHR-P population who do not transition to psychosis.[62] Similarly, depressive symptoms are also frequent in early stages of psychosis and can often be prolonged in time.[63]

Besides potentially being part of a CHR-P presentation, PD symptoms in adolescence often precede manic episodes and therefore constitute symptoms of a bipolar disorder, with psychotic symptoms being a risk factor for developing a subsequent bipolar disorder.[64] Antidepressant medication can often trigger such manic affective switches when being prescribed to treat depression.[65] Manic affective switches were also observed to be triggered by ECT in some of the literature reviewed, where individuals presented with a treatment-emergent affective switch during the treatment of PD.[22]

Therefore, the concept of PD in itself is likely a heterogeneous entity, with some PD presentations in adolescence likely to lead to future diagnoses of bipolar disorder or psychosis.[66–68] Further research is needed in order to further understand and characterize these presentations and predict future diagnostic trajectories.

On the other hand, some individuals, particularly those with a history of trauma, can also experience atypical, fleeting, or situationally specific hallucinations. It is important to differentiate such experiences from psychotic symptoms in clinical practice, given the differences in resulting diagnosis (more frequently an anxiety disorder or a non-psychotic mood disorder) and subsequent treatment options.[63]

Some limitations of our research must be noted, particularly related to the amount of evidence available in the literature and the consequent non-systematic approach and focus on other related but not exact conditions for the recommendations. Evidence in adolescent population with psychotic depression is very limited and only available from non-controlled studies and case reports or case series. Due to the scarcity of available literature, some articles included use treatments no longer aligning with current clinical practice, such as TCA.

Diagnoses were often based on the clinical impression of the treating clinician and not confirmed through a second opinion. The reviews published on the treatment of BD in adolescents also highlighted the lack of non-industry sponsored trials as a potential risk for bias. Finally, evidence found for adolescent psychotic depression is old and includes medication not routinely used currently for the treatment of C&A such as TCAs and first-generation antipsychotics.

Conclusion

Our review obtained evidence to endorse certain treatment options for psychotic depression in adolescents, such as the antidepressant-antipsychotic combination like OFC, or antidepressant monotherapy for presentations with lower symptoms severity. ECT can be considered for treatment-resistant cases or adolescents unable to take medication or needing a quick treatment response. Psychological therapy is also likely to have a positive impact in the treatment of psychotic depression in adolescents. This work highlights the need for studies (particularly randomized clinical trials) evaluating the efficacy and tolerance of currently commonly prescribed pharmacological interventions (eg SSRIs and second-generation antipsychotics) and psychological interventions in adolescents. Given the significant impact of psychotic depression in this population, further research on effective and safe treatments must be prioritized in coming years.

Abbreviations

ICD, International Classification of Diseases; DSM, Diagnostic and Statistical Manual of Mental Disorders; NICE, National Institute for Health and Care Excellence, BD, Bipolar depression; AACAP, American Academy of Child and Adolescent Psychiatry; CANMAT, Canadian Network for Mood and Anxiety Treatments; BAP, British Association for Psychopharmacology; OFC, Olanzapine-fluoxetine combination; C&A, Children and adolescents; ECT, Electroconvulsive therapy; TCA, Tricyclic antidepressants; BNFC, British National Formulary for Children; TSH, thyroid stimulant hormone; SSRI, selective serotonin reuptake inhibitor; FFT, family-focused treatment; CFF-CBT, Child- and Family-Focused Cognitive Behavioral Therapy; GAD, generalized anxiety disorder; n.a, not available; PTSD, post-traumatic stress disorder.

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