**Current and potential pharmacological and psychosocial interventions for anxiety symptoms and disorders in patients with schizophrenia: structured review**

**Running title:**

Interventions for anxiety in schizophrenia

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**ABSTRACT**

OBJECTIVE: Between 30-62% of patients with schizophrenia present with co-morbid anxiety disorders which are associated with increased overall burden. Our aim was to summarise current and potential interventions for anxiety in schizophrenia.

DESIGN: Structured review, summarizing pharmacological and psychosocial interventions used to reduce anxiety in schizophrenia and psychosis.

RESULTS: Antipsychotics have been shown to reduce anxiety, increase anxiety, or have no effect. These may be augmented with another antipsychotic, anxiolytic or antidepressant. Novel agents, such as L-theanine, pregabalin, and cycloserine show promise in attenuating anxiety in schizophrenia. Psychosocial therapies have been developed to reduce the distress of schizophrenia. Cognitive behavioural therapy (CBT) has shown benefit and refinements in the therapy have been successful, e.g. for managing worry in schizophrenia. CBT usually involves more than 16 sessions, as short courses of CBT do not attenuate the presentation of anxiety in schizophrenia. To address time and cost the development of a manualized CBT to address anxiety in schizophrenia is being developed.

CONCLUSIONS: The presence of coexisting anxiety symptoms and comorbid anxiety disorders should be ascertained when assessing patients with schizophrenia or other psychoses as a range of pharmacological and psychosocial treatments are available.

**Background**

Many attempts have been made to explain the presence of anxiety disorders in patients with schizophrenia. Anxiety may be regarded as an ‘understandable’ response to the distressing nature of the psychotic state (Hafner et al., 1992,Shaw et al., 1997). Anxiety symptoms may predate the onset of psychosis (Hofmann, 1999,Turnbull and Bebbington, 2001) or develop following remission of psychotic symptoms, with or without antipsychotic treatment (Pallanti et al., 2000,Ciapparelli et al., 2007). Family environmental and/or genetic factors which contribute to the risk of schizophrenia do not increase the risk of anxiety disorders to the same extent that the risk of anxiety disorders is increased by the presence of schizophrenia (Lyons et al., 2000). A twin study which compared twin pairs where neither was affected with schizophrenia, to twin pairs where one individual had schizophrenia reported a higher prevalence of anxiety disorders in the twins whose co-twin had a diagnosis of schizophrenia (Argyropoulos et al., 2008).

Co-morbid anxiety disorders in schizophrenia have been associated with delusions and hallucinations (as assessed by the positive symptom sub-scale within the Positive and Negative Syndrome Scale (PANSS)) (Tibbo et al., 2003,Mazeh et al., 2009), and in their absence with poor general mental health (general psychopathology sub-scale of the PANSS) (Tibbo et al., 2003). Further, features of social anxiety such as social avoidance and withdrawal, have been associated with negative symptoms (negative symptom sub-scale of the PANSS) (Mazeh et al., 2009). The varying nature of the association with the PANSS subscales suggests that anxiety and psychosis are separable constructs (Cooper et al., 2016,Michail and Birchwood, 2009).

The prevalence of anxiety disorders in patients with psychosis ranges between 30-62% (Goodwin et al., 2003,Pallanti et al., 2004,Braga et al., 2004,Huppert and Smith, 2005,Karatzias et al., 2007,Nebioglu and Altindag, 2009,Braga et al., 2013). Common co-morbid anxiety and related disorders in schizophrenia include social phobia/anxiety disorder, post-traumatic stress disorder (PTSD), obsessive-compulsive disorder (OCD), generalized anxiety disorder (GAD), and panic disorder (for comprehensive reviews see (Braga et al., 2004,Braga et al., 2013,Buckley et al., 2009,Achim et al., 2011). A meta-analysis which addressed the prevalence of comorbid anxiety disorders in schizophrenia found that social phobia is the most prevalent anxiety disorder (14.9%), followed by PTSD (12.4%); OCD (12.1%); GAD (10.9%); and panic disorder (9.8%) (Achim et al., 2011). In children with early onset schizophrenia there is a reported association with separation anxiety (Ross et al., 2006,Bailly and de Chouly de Lenclave, 2004).

Prodromal presentation with anxiety is reported to affect 8% of individuals, significantly lower than presentation with depression (40%) (Fusar-Poli et al., 2014). Using assessments that measure aspects of anxiety, such as the Present State Examination, individuals specifically report increased ‘situational anxiety’ and ‘tension’ (Owens et al., 2005). When employing the Early Recognition Inventory, individuals reported ‘introversive withdrawal’ (social withdrawal, shyness) and ‘dysphoria’ (irritability, tension) (Raballo et al., 2014). When predicting vulnerability to the development of schizophrenia the presentation of dysphoria and introversive withdrawal are key prodromal symptoms, while differential intensity of paranoid autocentrism and disturbed subjective experience can be present (Raballo et al., 2014). The presentation of anxiety symptoms prodromally however is not able to predict the transition to psychosis (Fusar-Poli et al., 2014). The presence of anxiety symptoms in the prodromal state have been associated with subsequent poorer general function (Fulford et al., 2013) and greater likelihood of suicidality/self-harm behaviours (Fusar-Poli et al., 2014) once a diagnosis of schizophrenia diagnosis has been made.

Severe anxiety symptoms are not uncommon in outpatients with psychotic disorders (Steer et al., 2003). The presence of coexisting anxiety symptoms and comorbid anxiety disorders adversely affects prognosis, reduces quality of life (Pallanti et al., 2004,Huppert and Smith, 2005,Fenton and McGlashan, 1986,Braga et al., 2005), can contribute to suicidality (Pallanti et al., 2004,Potkin et al., 2003), and complicate clinical management (Buckley et al., 2009). For example, co-morbid social anxiety can worsen social withdrawal, a negative symptom of psychosis, as it can highlight feelings of shame related to having a diagnosis of schizophrenia (Birchwood et al., 2007). A second example, anxiety has been associated positively with insight to their psychotic illness, which again was shown to reduce quality of life {{1623 Wiffen,B.D. 2010; 1620 Gharabawi,G.M. 2006; 1441 Huppert,J.D. 2005}}.

Neuroimaging studies of anxiety in schizophrenia are limited, though several interesting associations have been identified. Increased anxiety in schizophrenia was found to be correlated with glucose metabolism in the right medial frontal cortex and left thalamus, whereas in healthy controls anxiety was correlated with left frontal and parietal hemisphere glucose metabolism (Wik and Wiesel, 1991), suggesting a different network is involved in the presentation of anxiety in schizophrenia. Anxiety in schizophrenia was found to be negatively correlated with serotonin-1A receptor binding: individuals with schizophrenia showed a 19% reduction in serotonin-1A receptor binding, when compared to controls (Yasuno et al., 2004), suggesting a different allostasis of the serotonergic system. A structural MRI study found hypothalamic structures, specifically the mammillary bodies, were enlarged and correlated with increased anxiety (Tognin et al., 2012). A 31-phosporus magnetic resonance spectroscopy study found right frontal lobe phosphodiesters and right frontal lobe phosphocreatine to be strongly correlated with anxiety symptoms in schizophrenia (Deicken et al., 1994), suggesting altered energetics/metabolism. A recent study of short-range and long-range resting state brain network efficiency showed anxiety in schizophrenia to be correlated with decreased global efficiency in brain networks, specifically long-range network efficiency, but found short-range networks to be hyperactive (Su et al., 2015). Children with chromosome 22q11.2 deletion, of which 30-41% develop a psychotic disorder (Schneider et al., 2014,Green et al., 2009,Gambini, 2016), were found to have reduced hippocampal volume and shape variation, greater inward deformation of the anterior hippocampi being associated with increased anxiety (Scott et al., 2016). Taken together, these studies suggest altered patterns of activation and dysfunction of specific networks which might underlie anxiety in schizophrenia, and further imaging studies are clearly warranted.

The design of the current structured review was to summarize pharmacological and psychosocial interventions that have attempted or succeeded to reduce anxiety in schizophrenia and psychosis.

**Pharmacological treatment of anxiety in schizophrenia**

The presence of anxiety symptoms or disorders in patients with schizophrenia is often under-recognised and clinical guidelines are needed (Tibbo et al., 2003,Townsend and Wilson, 2005). Improved study designs are needed to assess the potential effects of psychotropic drugs (Buchanan et al., 2010,Dold et al., 2012).

Anxiety symptoms and disorders appear more prevalent among psychotic patients who are undergoing treatment with multiple psychotropic drugs (Chakos et al., 2006). Antipsychotic treatment has been reported to either decrease or increase presentation of anxiety in schizophrenia (Buckley et al., 2009). Anxiety may increase with ‘typical’ (first-generation) antipsychotic treatment when compared with ‘atypical’ (second generation) antipsychotic treatment: haloperidol vs. risperidone (Ceskova and Svestka, 1993,Janicak et al., 2009); haloperidol vs. clozapine (Kane et al., 2001)).However other studies found the converse (risperidone vs. haloperidol (Azorin, 1995)), some studies suggest that typical and atypical antipsychotic drugs are both anxiogenic: haloperidol and iloperidone (Kane et al., 2008); aripiprazole (Swainston Harrison and Perry, 2004); chlorpromazine and reserpine (Sarwer-Foner and Ogle, 1956); risperidone in first episode patients (Sannomiya et al., 2003); clozapine (Pallanti et al., 1999); and lurasidone (Citrome et al., 2014)). Other studies have found that typical or atypical antipsychotics are anxiolytic: olanzapine (Ishigooka et al., 2001); risperidone (Mesotten et al., 1989,Castelao et al., 1989); clozapine (Tibbo and Gendemann, 1999); lurasidone (Loebel et al., 2015). Amongst atypical antipsychotics, some appear more effective in treating anxiety symptoms, although not all evidence is consistent (olanzapine vs. quetiapine or risperidone (Mayoral et al., 2006); risperidone vs. olanzapine (Conley and Mahmoud, 2001); risperidone vs. aripiprazole (Janicak et al., 2009)). A recent study of anxiety symptoms in patients with first episode schizophrenia found that there was no attenuation in anxiety symptoms with use of either typical (haloperidol 2 week discharge) or atypical (olanzapine 3 week discharge) antipsychotics, and reduction of anxiety did not influence discharge rates (Rasmussen et al., 2016).

The antipsychotic [ziprasidone](http://www.ncbi.nlm.nih.gov/pubmed/11978164) showed promise in ameliorating co-morbid anxiety disorders in schizophrenia. One study reported decreased general anxiety in patients with schizophrenia and co-morbid obsessive-compulsive disorder (Juven-Wetzler et al., 2014). Another reported improved prosocial behaviour, assessed with the PANSS, during treatment with ziprasidone (Loebel et al., 2004). Another reported no change in anxiety with ziprasidone, whereas clozapine was found to increase anxiety (de Araujo et al., 2014). It has been suggested that ziprasidone may be a useful augmenting agent in children with schizophrenia and comorbid anxiety symptoms/disorder (Toren et al., 2004).

When given as a long acting injectable atypical antipsychotic, risperidone was found to reduce PANSS anxiety cluster scores in patients with schizoaffective disorder (Lasser et al., 2004,Mohl et al., 2005). Studies of long acting injectable risperidone conducted prior to 2004 found no increase in reported anxiety (Hosalli and Davis, 2003,Martin et al., 2003). However, long acting risperidone may be associated with an increase in reported anxiety symptoms (from 12.3% to 17.3%) in patients with longer duration of illness (3 or more years) (Macfadden et al., 2010), and another study reported a 24% increase in anxiety (Fleischhacker et al., 2003). Anxiety is one of many potential adverse events of long acting injectable antipsychotics, occurring in more than 5% of individuals (Fleischhacker et al., 2013,Mitchell et al., 2013,Wang et al., 2014,Parellada et al., 2010,Marinis et al., 2007). A recent meta-analysis of randomized controlled trials with oral and long-acting injectable atypical antipsychotics(risperidone and paliperidone)found that long-acting injectable antipsychotics were associated with increased anxiety when compared to oral dosing of either atypical antipsychotic investigated (Misawa et al., 2016). Increased anxiety has been reported in 10.6% of individuals receiving injectable paliperidone (Alphs et al., 2015a), and a comparative study with oral paliperidone found that injectable paliperidone was associated with an increase in anxiety (12%) significantly more frequently than was oral paliperidone (6%) (Alphs et al., 2015b).

Antipsychotic switching studies provide additional insights into the effects of medication on anxiety. Switching studies, primarily from typical to atypical have shown a reduction in anxiety and psychotic symptoms (olanzapine (Noordsy et al., 2001); risperidone or olanzapine after 2-6 years (Voruganti et al., 2002); risperidone or olanzapine after 8-weeks in elderly (Jeste et al., 2003)), whereas others have reported an increase in anxiety (7.4%) with increased psychotic symptoms (11.7%) (haloperidol to olanzapine after 6-weeks (Costa e Silva et al., 2001)). Some studies have found increased efficacy for some atypical antipsychotics (risperidone vs. olanzapine after 22 weeks, with comparable attenuation of psychotic symptoms - (Wang et al., 2006); olanzapine to risperidone due to incompatibility, accompanied by attenuation of psychotic symptoms (Ganguli et al., 2008)). Care should be taken when switching antipsychotic medications, as this may lead to development of anxiety (Borison, 1996,Delassus-Guenault et al., 1999,Poyurovsky et al., 1998).

Augmentation of antipsychotic medication is a common clinical approach to reduce anxiety symptoms or treat co-morbid anxiety disorders, with either another antipsychotic (olanzapine with sulpiride (Kotler et al., 2004)), an antidepressant (clozapine with sertraline for attenuation of OCD symptoms (Rahman et al., 1998,Allen and Tejera, 1994)), or anxiolytic drug (benzodiazepine over short-term, with consideration of potential addictive properties (Nuss et al., 2007)). Studies have found evidence for the beneficial effects of fluoxetine for social phobia (Pallanti et al., 1999); fluoxamine for OCD (Poyurovsky et al., 1996,Reznik and Sirota, 2000); and for a broad spectrum of anxiolytics (Braga et al., 2013,Acquaviva et al., 2005)) in psychotic disorders. Careful consideration of potential risks of pharmacokinetic or pharmacodynamic interactions and cardiac safety is needed (Sicouri and Antzelevitch, 2008,Hoehns et al., 2001). Antidepressant and anxiolytic medications have not been shown to reduce suicidality (Dold et al., 2012,Krupinski et al., 2000,Sim et al., 2014): only the antipsychotic clozapine has been shown to reduce suicidality in schizophrenia (Mamo, 2007,Glick et al., 2004).

There is limited data on the efficacy of antipsychotic medications in children and whether presentation with anxiety precedes or promotes psychotic symptoms. Antipsychotic medications (risperidone, quetiapine, and aripiprazole) have been associated with presentation of anxiety when prescribed to children (Aparasu and Bhatara, 2007). Girls appear more likely to receive antipsychotic medications for an anxiety disorder than boys (Nesvag et al., 2016). Atypical antipsychotics, olanzapine and ziprasidone may be beneficial in the treatment of psychotic symptoms and co-morbid anxiety symptoms in childhood schizophrenia {{1607 Ross,R.G. 2003; 1718 Toren,P. 2004}}. Anorexia nervosa in childhood is known to present with both psychotic symptoms and significant anxiety, here again the use of olanzapine has been shown to attenuate the psychotic symptoms and anxiety (Fremaux et al., 2007,Dadic-Hero et al., 2009).

The prevalence of smoking in patients with schizophrenia is significantly greater than in patients with other mental disorders and in the general population (Lohr and Flynn, 1992). It has been suggested that tobacco smoking is a form of ‘self-medication’ in patients with schizophrenia (Kumari and Postma, 2005). Anxiety symptoms and psychotic symptoms may worsen with smoking cessation in schizophrenia (Dalack and Meador-Woodruff, 1996). Presentation of similar nicotine dependence in schizophrenia with or without comorbid OCD showed no difference in Yale–Brown Obsessive Compulsive Scale scores, suggesting that nicotine was not a driver in presentation of anxiety symptoms (Fawzi et al., 2007). The siblings of individuals with a diagnosis of schizophrenia show a higher prevalence of smoking when compared to unaffected sibling pairs, which suggests that the presence of smoking is more likely a result of psychosocial factors, and not due to the presence of schizophrenia (Smith et al., 2008). Subjective reports from individuals with diagnosis of schizophrenia spectrum disorders indicate that a common reason for smoking was to reduce feelings of anxiety (Esterberg and Compton, 2005). Another study found that individuals with diagnosis of schizophrenia found smoking to have a calming effect and a sociability effect, which was associated with a reduction in negative symptoms (Gurpegui et al., 2007). It remains uncertain whether nicotine cigarette smoking attenuates or perpetuates anxiety in schizophrenia (Smith et al., 2002,Araki et al., 2002,Tidey and Miller, 2015). A single feasibility study found that with counselling and exercise, motivation to reduce smoking was achievable, and there were no changes in anxiety (Bernard et al., 2013).

Many novel agents are being investigated for the treatment of anxiety in schizophrenia (Garay et al., 2015). The amino-acid L-theanine showed promise in the reduction of anxiety in schizophrenia, in an 8-week randomized double-blind placebo-controlled 2-center study (Ritsner et al., 2011). Both L-theanine and pregnenolene have been shown to augment antipsychotic treatment with efficacy in the attenuation of anxiety symptoms (Kardashev et al., 2015): and the anxiety attenuating effects of L-theanine have been associated with increased serum-brain derived neurotrophic factor and cortisol (Miodownik et al., 2011). Other potential pharmacological interventions include the cannabis derivative cannabidiol (Blessing et al., 2015,Pushpa-Rajah et al., 2015) and the glycine-reuptake inhibitor bitopertin (Rofail et al., 2016). Pregabalin, an antagonist at the alpha-2-delta subunit of voltage-gated calcium channels, has been shown to attenuate anxiety in schizophrenia (Englisch et al., 2010), but further evaluation is needed as it may potentiate clozapine serum levels and contribute to falls (Schjerning et al., 2015). d-Cycloserine has been shown to promote neuroplasticity via enhancement of NMDA receptor function, and may enhance the effectiveness of cognitive and behavioural therapies which has potential value in the overall management of patients with schizophrenia, including the presentation of anxiety (Krystal et al., 2009,Otto et al., 2015). It has also been shown to promote the efficacy of some antipsychotics (olanzapine and risperidone (Heresco-Levy et al., 2002)).

It is worth considering potential target sites for gene therapy in the treatment of schizophrenia with an anxiety disorders. This principle is the introduction of ‘normal genes’ into cells where ‘dysfunctional genes’ have been identified. These target genes could include -141C Ins/Del DRD2 polymorphism (Suzuki et al., 2001,Kondo et al., 2003), COMT Val(158)Met polymorphism (Zinkstok et al., 2008), CYP2D6 polymorphism (Dorado et al., 2007), and 5-HTTLPR polymorphism of the 5’ promoter region of serotonin transporter gene (SLC6A4) (Goldberg et al., 2009). However there are many technical difficulties in application of gene therapy, and it will prove challenging to apply gene therapy to this complex and psychiatric presentation, e.g. schizophrenia with an anxiety disorder (Weatherall, 1995).

**Psychosocial interventions for anxiety in psychosis**

Early psychosocial therapies primarily addressed the positive and negative symptoms of schizophrenia. More recent research has started to address the presentation of anxiety in schizophrenia. One such intervention, cognitive behavioural therapy (CBT), aims to reduce catastrophic appraisals, thereby reducing concurrent anxiety and distress (Sommer et al., 2012). Successful management of anxiety symptoms involves the adoption of appropriate coping strategies that reduce anxiety and there is emerging evidence that this may also reduce core symptomatology of psychosis {{1566 Malcolm,C.P. 2015; 1483 Mankiewicz,P.D. 2014; 1454 Docherty,N.M. 2011}}.

It has been suggested that therapy with family members serves to reduce the adverse effects of criticism by influential family members, which is known to exacerbate anxiety and psychotic symptoms (Docherty et al., 2011). Interventions where family members were included have been shown to assist family members in understanding psychosis, but not to improve the outcome for the individual with psychosis (Okpokoro et al., 2014). Befriending interventions for young people with psychosis, in which the therapist works with the patient’s social group to maintain social continuity, may be beneficial in the reduction of anxiety within these schizophrenia (Harrop et al., 2014), study is required to ascertain the benefits of befriending in schizophrenia and its potential role in reducing anxiety.

Body-mind interventions including the use of exercise and mindfulness techniques appear promising. Aerobic exercise effectively decreased state anxiety in schizophrenia (Oertel-Knochel et al., 2014). Dance therapy which uses dance and movement to explore emotions in a non-verbal way improved negative symptoms, although its effects did not endure, partly due to high drop-out rates (Xia and Grant, 2009). When compared with physical training, yoga therapy was found to be superior, with greater effects on general psychopathology, social function, occupational function and quality of life in patients with schizophrenia at 4 months (Duraiswamy et al., 2007). However an investigation of Hatha yoga found no effect as measured by the PANSS, and no change in the level of ‘resilience’ or on biological measures of stress (Ikai et al., 2014). Mindfulness therapy was found to improve the response to stressful internal events in psychosis (Langer et al., 2012), with increased emotion regulation and decreased affective symptoms (Khoury et al., 2013). Although no adverse effects have been reported in the use of these interventions (Xia and Grant, 2009,Chadwick, 2014) further research with more refined interventions are needed, i.e. not only address the positive and negative symptoms of schizophrenia and the broad affective symptoms, but should address the presentation of anxiety in schizophrenia, in the short and long-term. A recent study which integrated cognitive therapy with mindfulness to address distressing voices in psychosis found a reduction in the intensity of voice distress but it did not reduce anxiety distress (Chadwick et al., 2016).

A therapy aimed at improving neurocognition in schizophrenia, cognitive remediation therapy (CRT), employed CBT as a control therapy. CBT showed an improvement in anxiety and depressive symptoms, while CRT showed significant improvement in neurocognition, particularly within the working memory domain, and improved social function (Penades et al., 2006). Treatment of PTSD in schizophrenia with CBT for PTSD was found to effectively alleviate the patients (12/13) of necessary criterion to meet the diagnosis of PTSD (Frueh et al., 2009). A recent study which examined the in-session ‘process’ of working alliance and emotional processing of trauma memories in individuals with schizophrenia (TF-CBT), found that a working alliance was established, but not to the level that would facilitate successful cognitive restructuring (O'Driscoll et al., 2015).

CBT has been shown to reduce relapse in psychosis (Gumley et al., 2003,Turkington et al., 2008,Kingdon and Turkington, 1991). Successful CBT involves the reduction of distress, through problem solving, modifying distorted thinking, and reducing dysfunctional behaviour. CBT for psychosis (CBTp) pays particular attention to reducing distress associated with positive symptoms of psychosis (Wright et al., 2009) and has been shown to have beneficial effects in reducing anxiety symptoms in patients with first episode psychosis (Welfare-Wilson and Newman, 2013) and more enduring schizophrenia with a brief insight-focused intervention (Naeem et al., 2006). A CBTp study which involved 16 sessions, focused primarily on cognitive restructuring of paranoid appraisals of auditory hallucination and behavioural experiments employed progressively via graded exposure to anxiety-inducing stimuli, was found beneficial in patients with paranoid schizophrenia and co-morbid anxiety disorders, as it attenuated paranoia, anxiety, and improved psychosocial functioning (Mankiewicz and Turner, 2014). A recent multi-centre randomized control trial found that CBTp, given as 15 sessions over 24 weeks, improved positive symptoms, insight and social functioning over the longer term, up to 60 weeks post-intervention (Li et al., 2015). A six session, 12 week CBTp intervention designed to reduce negative and increase positive self-cognitions, found a reduction in negative self-beliefs, improvements in psychological well-being, positive beliefs about self, reduced negative social comparison, self-esteem, and depression, but no change in anxiety, and reported improvements were not maintained (Freeman et al., 2014). Another augmentation CBTp intervention focused on the management of worry associated with paranoid delusions (Freeman et al., 2015): worry was described by the authors thus,“… an expectation of the worst happening. It consists of repeated negative thoughts about potential adverse outcomes, and is a psychological component of anxiety. Worry brings implausible ideas to mind, keeps them there, and increases the level of distress” (Freeman et al., 2015). From this they suggested that worry may be causal factor in the occurrence of persecutory delusions (Startup et al., 2016). A six session worry-reduction intervention produced reductions in worry and delusional conviction: the positive decrease in worry (cognitive component of anxiety) accounted for 66% of the positive change in the presentation of delusions (Freeman et al., 2015).

CBT for co-morbid anxiety disorders in psychotic disorders appears promising, with effects such as the attenuation of symptoms of social anxiety (Halperin et al., 2000,Michail et al., 2014), panic disorder (Arlow et al., 1997,Erickson et al., 2007), and OCD (Hagen et al., 2014), with associated improvements in quality of life (Arlow et al., 1997). However, a recent study addressing PTSD in schizophrenia found no reduction of PTSD related symptoms with CBT, positive effects were found simply with elapsed time from the trauma, the authors suggest that further adaptations of cognitive-restructuring programmes, such as CBT, are required to improve emotional processing of traumatic memories in the psychotic disorders (Steel et al., 2016).

Aside from the differing foci of CBT-related interventions, there is uncertainty about what is the optimal ‘dosage’ of CBT for schizophrenia (Gold, 2015,Hazell et al., 2016), though in general a greater number of sessions is associated with a greater chance of more lasting effects. Single sessions of CBT can be used as a ‘top-up’ session to manage any crises that might arise. CBT is often seen as a ‘labour’ or ‘clinically’ intensive intervention, although the evidence shows the lasting long-term benefits of brief interventions (Turkington et al., 2008) with some evidence of cost-effectiveness (Turkington et al., 2006). In contrast, another study of low-intensity CBT for psychosis found it did not reduce anxiety symptoms in schizophrenia (Waller et al., 2013). Together these have led to the development of a manualized CBT intervention to specifically address anxiety and depression in psychosis by establishment of a personal recovery goal (Waller et al., 2014). Self-guided manuals and apps to deliver CBT in psychosis are being developed to determine their efficacy, as has already been shown for eating disorders (Carrard et al., 2011,Striegel-Moore et al., 2010,Morrison et al., 2014).

An interesting paradigm is that of enhancing or strengthening resilience in individuals with psychosis so that they become less susceptible to developing anxiety and depressive symptoms (Bozikas and Parlapani, 2016). A four-step strengths-based CBT has been developed to help build personal resilience and reduce personal distress (Padesky and Mooney, 2012). A CBT study aimed at enhancing resilience in high risk adolescents with alcohol dependent parents, showed improved resilience (Hyun et al., 2010). Albeit that these studies were not performed in the context of anxiety in schizophrenia, it does not limit the inclusion or building resilience in CBTp. The development of enhanced resilience may serve to reduce anxiety in schizophrenia and other psychoses (Bozikas and Parlapani, 2016).

In conclusion, this structured review addresses the current and novel pharmacological and psycho-social interventions in psychotic disorders when coexisting anxiety symptoms and comorbid anxiety disorders are present. The management of anxiety in patients with psychotic disorders has been shown to reduce the severity and distress of symptoms related their psychosis. Further research is needed to deepen our understanding of the brain networks involved, which may lead to improve therapies. Currently, there are a range of pharmacological and psychosocial treatments available and should be applied to reduce the presentation of anxiety in psychotic disorders.

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