

Oxytocin system dysfunction as a common mechanism underlying metabolic syndrome and psychiatric symptoms in schizophrenia and bipolar disorders

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Abstract

There is growing interest in using intranasal oxytocin (OT) to treat social dysfunction in schizophrenia and bipolar disorders (i.e., psychotic disorders). While OT treatment results have been mixed, emerging evidence suggests that OT system dysfunction may also play a role in the aetiology of metabolic syndrome (MetS), which appears in one-third of individuals with psychotic disorders and associated with increased mortality. Here we examine the evidence for a potential role of the OT system in the shared risk for MetS and psychotic disorders, and its prospects for ameliorating MetS. Using several studies to demonstrate the overlapping neurobiological profiles of metabolic risk factors and psychiatric symptoms, we show that OT system dysfunction may be one common mechanism underlying MetS and psychotic disorders. Given the critical need to better understand metabolic dysregulation in these disorders, future OT trials assessing behavioural and cognitive outcomes should additionally include metabolic risk factor parameters.

Keywords: Metabolic syndrome, Oxytocin, Schizophrenia, Bipolar disorders, Cognition, Antipsychotic

1. Introduction

Shortened life span in schizophrenia and bipolar disorders (defined here as psychotic disorders) related to increased risk for cardiovascular disease (CVD) is a considerable societal challenge. One-third of patients with psychotic disorders suffer from metabolic syndrome (MetS) (Mitchell et al., 2013), which is a collection of metabolic risk factors predictive for the development of CVD and type 2 diabetes mellitus (T2DM). These risk factors include insulin resistance, increased blood pressure, visceral adiposity, elevated triglyceride levels, and reduced high-density lipoprotein cholesterol levels (Grundy et al., 2005). Despite the increased risk of death from CVD in males (Berry et al., 2012), there is a comparable prevalence of MetS in male and female patients with psychotic disorders (Mitchell et al., 2013), as per the general population (Ford et al., 2002; Park et al., 2003). Compared to individuals showing no evidence of metabolic dysfunction, people with MetS have a 2-fold risk of premature mortality due to increased risk of cardiovascular diseases (Gami et al., 2007), several cancers (Esposito et al., 2012), and T2DM (Hanley et al., 2005). MetS is twice as prevalent in patients with psychotic disorders as the general population (Birkenaes et al., 2007), and the link between MetS and increased risk of early mortality urgently calls for a better understanding of the etiology of MetS and its overrepresentation in psychotic disorders. Along with lifestyle habits such as smoking, poor diet and a lack of exercise (Daumit et al., 2005; McCreadie, 2003), some antipsychotic medications, such as olanzapine and clozapine, account for some of the increased prevalence of MetS risk factors in patient groups (Fontaine et al., 2001). However, evidence of MetS risk factors in untreated individuals with first-episode psychosis (Venkatasubramanian et al., 2007a), healthy first-degree relatives (Fernandez-Egea et al., 2008), and in patients prior to the introduction of

antipsychotics (Raphael and Parsons, 1921) suggest that the MetS is, in part, independent from antipsychotic treatments. While genetic studies support a shared predisposition between MetS and psychotic disorders (Andreassen et al., 2014), the precise physiological mechanisms underpinning the shared risk for psychotic disorders and MetS remain unclear. However, emerging evidence suggests that oxytocin (OT) system dysfunction plays an important role in the etiology of both psychotic disorders and MetS. Here we review this evidence from preclinical research and studies in clinical populations and suggest future lines of investigation to move the field forward towards a better understanding of the role of somatic factors in psychotic disorders. Reviews and original research papers were considered for inclusion in the review according to the authors' knowledge of the field and Pubmed and Google Scholar search results with the following combination of terms: (oxytocin) AND (metaboli* OR MetS) AND (schizophreni* OR bipolar OR psycho*) AND (metaboli* OR MetS). Reference lists were also reviewed to identify any additional relevant literature.

2. The oxytocin system in psychotic disorders

Research on the neurobiology of social cognition and behaviour has revealed a central role of the neuropeptide OT. Early animal studies demonstrated that the OT system is critical for many facets of mammalian social behavior, including maternal behavior, sexual behaviors, and pair bonding (Carter, 1992; Insel, 1992; Pedersen et al., 1994). These results were subsequently bolstered by OT gene knockout mice showing striking effects on social memory and recognition, with central OT administration reversing these deficits (Winslow and Insel, 2002). Brain region-specific OT receptors and neurons have also been shown to modulate social behaviors

(Bale et al., 2001). Owing to these results, research began to investigate the effects of OT on social behavior in humans, with impressive effects. For instance, a single administration of intranasal OT was shown to improve emotion recognition, increase gaze to the eye region, and increase attention to socially relevant information (Guastella and MacLeod, 2012). Early evidence indicates that OT system dysfunction is a potential risk factor for the development of psychotic disorders. For example, oxytocin pathway gene variants are associated with psychotic disorders (Montag et al., 2013), which also appear to underpin emotion processing (Haram et al., 2016), and social cognition performance (Davis et al., 2014b). Intranasal OT administration has been shown to target three key symptom domains of psychotic disorders by improving positive symptoms (e.g., delusions, thought disturbances) (Feifel et al., 2010), negative symptoms (e.g., deficits in motivation and emotion) (Lee et al., 2013), and cognitive deficits in working memory (Michalopoulou et al., 2015) and social cognition (Davis et al., 2014a). Converging evidence indicates that these symptom improvements are underpinned by the effect of exogenous OT on social brain circuitry (Bethlehem et al., 2013). These results have led to randomized controlled trials (RCTs) investigating its potential application in the treatment of various psychiatric disorders (for a review of published registered trials, see Quintana et al., 2016a). For instance, an RCT in male and female children with autism reported that five weeks of intranasal OT treatment led to significant improvements in caregiver-rated social responsiveness (Yatawara et al., 2015). Leading theories suggest that OT exerts its effects by either increasing social salience (Bartz et al., 2011) or facilitating approach related behaviors (Kemp and Guastella, 2011), although both processes likely occur in tandem (Quintana et al., 2015a).

Despite these results, more recent work (Leng and Ludwig, 2016; Walum et al., 2016) has questioned the efficacy of OT to influence social behavior due to issues surrounding a poor understanding of mechanisms – primarily how OT reaches the brain and the dose-response – and potential publication bias. Moreover, there have been a number of OT studies that have failed to detect a difference from placebo (Dadds et al., 2014; Guastella et al., 2015), which is a considerable problem for drug discovery in general. Disparate experimental approaches, particularly surrounding intranasal OT administration methods, have been proposed as a source of this variation in OT response (Guastella et al., 2013; Quintana et al., 2016a). In an effort to better understand OT’s mechanisms and administration, research has compared different administration modalities (intranasal vs. intravenous) and intranasal dosages [8 international units (IU) vs. 24IU] in males revealing that the cognitive (Quintana et al., 2015b) and neural (Quintana et al., 2016d) effects of intranasal OT administration probably occur via direct nose-to-brain OT delivery (rather than transport across the blood-brain barrier via circulating blood) and that a lower 8IU dose may be more efficacious than the traditionally used 24IU dose. Moreover, recent efforts to ‘open the file draw’ of OT laboratories (Lane et al., 2016) and a steadily increasing rate of preregistered OT trials (Alvares et al., 2016b) will contribute towards the reduction of publication bias in this field, thus increasing the overall quality of research.

As the majority of participants in OT biobehavioral research have been males (e.g., 93% in autism; Alvares et al., 2016b) the moderating effect of sex on response to intranasal OT is poorly understood. Given that OT tends to fluctuate with estrogen levels (Dellovade et al., 1999; Sarkar et al., 1992), research studies recruiting females often collect all participant data during the same menstrual cycle phase to help avoid gonadal steroid confounds (e.g., Bertsch et al., 2013). The use of hormonal

contraceptives is also an important consideration in light of their dampening effect on neural responses to OT (Scheele et al., 2016). Well recognized non-human mammalian sex differences in neuropeptide function (Carter et al., 2009; Li et al., 2016; Scott et al., 2015), are also reflected in human studies. For instance, while neuroimaging studies suggest that intranasal OT decreases amygdala activity in males (Domes et al., 2007; Kirsch et al., 2005; Labuschagne et al., 2010; Petrovic et al., 2008; Quintana et al., 2016b), it appears to increase amygdala activity in females, even when controlling for menstrual cycle phase (Domes et al., 2010; Lischke et al., 2012). However, these opposite effects might only occur in neurotypical participants as a study in PTSD patients reported that OT reduces amygdala reactivity in both males and females (Koch et al., 2015). Human females also have increased central concentrations of OT compared to males (Altemus et al., 1999). However, there are no differences in brain OT receptor binding (Loup et al., 1991). Therefore, as most biobehavioral OT research has been conducted in males, researchers should be cautious when extrapolating these findings to female populations.

3. The oxytocin system and metabolic syndrome

In parallel to human research on OT's effect on social behavior and cognition, there is also a growing body of pre-clinical research implicating the OT system in MetS. The OT system has not only been shown to play an important direct role for specific MetS risk factors but also via processes that indirectly influence these risk factors, such as feeding behaviors (Arletti et al., 1989; Arletti et al., 1990; Lokrantz et al., 1997; Maejima et al., 2011; Olson et al., 1991a; Olson et al., 1991b).

3.1. Oxytocin and MetS risk factors

Antipsychotic naïve individuals with psychotic disorders tend to have increased intra-abdominal fat compared to controls, which is further augmented with antipsychotic treatment (Ryan et al., 2004). Animal research from as early as the 1960s demonstrated that OT has an insulin-like effect on adipose tissue (Mirsky et al., 1962; Pittman et al., 1961). Later studies found that OT administration protected against high fat diet-induced obesity in rodents (Blevins et al., 2016; Deblon et al., 2011; Zhang et al., 2013) and rhesus monkeys (Blevins et al., 2015). Relatedly, OT knockout mice have a preference for sucrose (Amico et al., 2005; Sclafani et al., 2007) and develop pre-diabetic changes independent of food intake (Camerino, 2009; Takayanagi et al., 2008). Anti-obesity effects have also been observed to continue after the discontinuation of OT treatment in animals (Blevins et al., 2015; Blevins et al., 2016; Maejima et al., 2011), consistent with proposed positive feedforward mechanisms of central OT (Moos et al., 1984; Neumann et al., 1994). Reported effects on weight loss (Zhang et al., 2013) may also occur via OT's impact on adipocytes, which express OT receptors (Boland and Goren, 1987). Importantly, it appears that OT specifically targets adipose tissue as OT treatment leaves lean mass unchanged (Altirriba et al., 2014).

Psychotic disorders are associated with an increased prevalence of hypertension (Bresee et al., 2010; Liao et al., 2011). Evidence suggests that OT may induce long term decrease in blood pressure in rats (Petersson et al., 1996), which was shown to persist for ten days after the completion of OT treatment. However, other work has shown these effects may be specific to males (Petersson et al., 1997) or failed to demonstrate any effects on blood pressure (Maejima et al., 2011). Photoactivating rat OT neurons also reduces blood pressure (Jameson et al., 2016). However, single (Lawson et al., 2015) or chronic doses in humans (Busnelli et al.,

2016; Dadds et al., 2014) do not appear to influence blood pressure. This may be due to the potential floor effects of including normotensive participants so further work in MetS patients is needed.

Although psychotic disorders are associated with reduced HDL cholesterol (Mitchell et al., 2013), there is little evidence that the OT system plays a functionally significant role in regulating HDL cholesterol. For instance, in obesity and T2DM there is no relationship between peripheral or central levels of OT and HDL cholesterol (Qian et al., 2014; Yu et al., 2015). However, one trial has reported a modest increase in HDL-cholesterol levels after intranasal OT treatment (Zhang et al., 2013). Even if OT treatment increased HDL cholesterol, pharmacologically increasing HDL cholesterol may not even improve CVD outcomes (Keene et al., 2014).

Individuals with reduced peripheral plasma OT are more likely to have high triglyceride levels (Yuan et al., 2016), although a study in 69 males and females revealed no significant relationship between CSF OT levels and triglycerides (Yu et al., 2015). However, subcutaneous OT administration in rhesus monkeys and central administration in rats reduced triglycerides (Blevins et al., 2015; Deblon et al., 2011). Chronic OT administration in humans also reduces triglyceride levels, but not at a statistically significant level (Lawson et al., 2015; Zhang et al., 2013).

Antipsychotic naïve individuals with psychotic disorders have a higher insulin resistance than healthy controls (Venkatasubramanian et al., 2007b), which tends to worsen over time with antipsychotic treatment (Melkersson et al., 2000). Research suggests that OT administration promotes glucose uptake and stimulates insulin secretion in animals and humans (Knudtson, 1982; Lawson et al., 2015; Paolisso et al., 1989). OT knockout mice also develop insulin resistance (Camerino,

2009). Research has also reported that both central and peripheral OT administration in rats reduces insulin resistance (Deblon et al., 2011). Increased levels of insulin-sensitive glucose transporter 4 mRNA in fat after OT administration (Eckertova et al., 2011) may contribute to these observed insulin sensitivity improvements.

3.2. *Oxytocin and feeding*

Antipsychotic treatment increases weight gain (Allison et al., 1999), which is associated with increased appetite and feeding (Kinon et al., 2005). Given the relationship between weight gain and MetS, interventions that can reduce appetite may reduce the risk of MetS development. One of the first studies on the effects of OT treatment on human feeding and metabolic processes in the 1970s detected an improvement of gastric motility in patients with post-vagotomy gastric atony after intravenous OT infusion (Hashmonai et al., 1979), which was later shown in healthy adults (Petring, 1989). These effects, along similar observations of OT's influence on gastrointestinal (GI) physiology (Ohlsson et al., 2004), have been attributed to OT receptors on the smooth muscle of the GI tract (Qin et al., 2009), and appears to be a dose-dependent effect (Holmes et al., 2013). Ancestral OT-like peptides anetocin and mesotocin have also been shown to regulate feeding and digestion in diverse species such as earthworms (Ukena et al., 1995) and birds (Jonaidi et al., 2003), respectively. Following this early work, a series of animal studies demonstrated that OT administered both intracerebroventricularly (ICV) and intraperitoneally (IP) inhibits food intake in a dose-dependent fashion (Arletti et al., 1989; Arletti et al., 1990; Lokrantz et al., 1997; Maejima et al., 2011; Olson et al., 1991a; Olson et al., 1991b), which has been attributed to activation of vagal afferent neurons (Iwasaki et al., 2015). Moreover, reductions of food intake have been associated with increased

blood plasma OT concentrations (Olson et al., 1991a; Olson et al., 1991b). These effects were most likely centrally mediated as the effective ICV dose was not effective when administered IP. A centrally administered OT receptor antagonist has also been shown to stimulate food intake (Blevins et al., 2004). It has been hypothesized that OT reduces food intake via the potentiation of inhibitory action on cholecystokinin (CCK) via the modulation of leptin (Blevins et al., 2004) and by its impact on peripheral satiety signaling on central receptors (Blevins et al., 2004; Gaetani et al., 2010). Brain regions known to be involved in appetite regulation, such as the dorsomedial and ventromedial hypothalamic nuclei, are also rich in OT receptors (Gould and Zingg, 2003). OT-deficient mice have been shown to overeat sucrose and carbohydrate solutions (Sclafani et al., 2007), which may be due to OT's role in satiation, as OT concentrations typically increase after a satiating meal (Lucio-Oliveira and Franci, 2012; Yamashita et al., 2013). Genetically ablating OT neurons in the PVN in rats also increases weight gain in rats on a high-fat diet (Wu et al., 2012). Chronic sucrose intake may also impair the OT system (Mitra et al., 2010), which would facilitate continued sucrose intake.

3.3. OT and human trials

Complementing the abovementioned animal research, two preliminary human studies have reported that a single administration of intranasal OT reduces food intake and improves insulin sensitivity in healthy men (Lawson et al., 2015; Ott et al., 2013). Eight weeks of intranasal OT has also been reported to reverse pre-diabetic changes (Zhang et al., 2013). These effects on appetite in humans may be due to OT's effects on leptin secretion, which regulates hunger and satiety (Dhillon et al., 2006; Mantzoros and Moschos, 1998). There has also been indirect evidence of

anorexigenic effects, with reports of reduced appetite in youth with ASD during a 12-week course of intranasal OT (Anagnostou et al., 2014). Observational research has also revealed a 40% reduction of central OT neurons in Prader-Willi syndrome (Swaab et al., 1995), which is characterized by overeating, obesity, pica, obsessive thoughts, and compulsive behaviors (Einfeld et al., 1999). Together, these lines of evidence indicate that OT system dysregulation may constitute a shared risk factor for MetS and psychotic disorders. Accordingly, there has been an increase in registered clinical trials investigating the efficacy of intranasal OT to treat metabolic risk factors. A review of the five most used clinical trial registries (clinicaltrials.gov; EU Clinical Trials Register; Australia and New Zealand Clinical Trials Registry; Iranian Registry of Clinical Trials; Japan Primary Registries Network) in June 2016 reflects the growing interest in examining the efficacy of OT to treat MetS (Table 1).

4. Common cognitive deficits and neurobiological factors in psychotic disorders and MetS

Although the causal direction is unclear, many cognitive and neurobiological factors are common to psychotic disorders and MetS (Fig. 1). For instance, MetS is associated with reduced cognitive functions across the lifespan, with worse effects in men (Yates et al., 2012). MetS has been associated with poorer memory (Cavalieri et al., 2010) and overall IQ (Hassenstab et al., 2010). An investigation of individual MetS risk factors in patients with schizophrenia revealed that poor performance on an attention task was associated with greater waist circumference, lower HDL levels, and higher triglyceride levels (Lindenmayer et al., 2012). Likely causes of poorer cognitive function in patients with MetS include impaired vascular reactivity (Yates et al., 2012) and reduced insulin sensitivity impairing neural transmission (Yaffe et al.,

2004). While research has established that psychotic disorders are associated with neurocognitive deficits (e.g., Simonsen et al., 2009), schizophrenia patients with MetS performing considerably worse compared to non-MetS patients on tests of processing speed, attention, and problem solving (Lindenmayer et al., 2012). Moreover, when examining each MetS risk factor individually, higher triglyceride levels, lower HDL levels, and greater waist circumference were associated with worse cognitive function (Lindenmayer et al., 2012).

In regards to neurobiological factors, altered autonomic nervous system (ANS) regulation is associated with T2DM (Carnethon et al., 2003), CVD (Liao et al., 1997), and MetS (Stuckey et al., 2014), with research indicating that ANS dysregulation may precede the development of MetS (Chang et al., 2010). Indeed, psychotic disorders are associated with ANS dysregulation (Alvares et al., 2016a; Quintana et al., 2016c) and demonstrate the largest effect sizes differences for ANS dysfunction compared to healthy controls across all psychiatric disorders (Quintana, 2016). OT also administration improves ANS regulation (Kemp et al., 2012). Poor ANS function, which is partly regulated by OT (Quintana et al., 2013), may inhibit insulin secretion from the pancreas, leading to impaired glucose uptake (Carnethon et al., 2006).

While a wealth of research has investigated brain function in psychotic disorders (e.g., Kaufmann et al., 2015; Yurgelun-Todd et al., 2000) and specific MetS risk factors (e.g., BMI, insulin sensitivity, obesity; Chen et al., 2014; García-García et al., 2013; Kullmann et al., 2012) and T2DM (Musen et al., 2012), only one investigation has examined brain activity in MetS to the best of our knowledge. In this study, Hoth and colleagues report that compared to healthy controls, individuals with MetS show reduced brain activity in the right superior frontal gyrus, right superior

parietal lobule, and left inferior parietal lobule in response to a working memory task (Hoth et al., 2011), for which the authors suggest could be due to impairments in vascular responsivity. While both psychotic disorders (Rimol et al., 2010; van Erp et al., 2015) and MetS are also associated with brain structure abnormalities (Song et al., 2015; Tiehuis et al., 2014; Yau et al., 2012), research has yet to delineate the independent effects on brain structure of psychotic disorders and MetS, respectively.

5. The etiology and measurement of oxytocin system dysfunction

Despite early evidence that the OT system is impaired in psychotic disorders (MacDonald and Feifel, 2012), there are a number of pressing questions surrounding the etiology and measurement of OT system dysfunction in this patient population with respect to metabolic function. Variations in the OT signal pathway genes have been associated with psychotic disorders (Montag et al., 2013) and the brain circuitry underlying social functioning (Tost et al., 2010). For instance, the OT receptor gene (OXTR) has been linked with prosociality (Ci et al., 2014) and empathic concern (Schneiderman et al., 2014). Research has also established an association between OXTR variations and a number of biological features that contribute to psychotic disorders susceptibility such as brain function (Tost et al., 2010), brain structure, and with ANS dysregulation in response to stressors (Norman et al., 2012). The CD38 gene, which modulates both OT and insulin secretion via Ca^{2+} signaling (Jin et al., 2007; Kato et al., 1995), has also been linked with social behavior (Chang et al., 2014) and T2DM (Yagui et al., 1998). Although there is a growing body of research on the impact of OT pathway gene single nucleotide polymorphisms (SNPs) on mental illness and psychological processes, research is yet to identify OT SNPs that are associated with MetS in psychotic disorders.

Relatedly, the role of OT concentrations in the brain compartment is poorly understood (Leng and Ludwig, 2016). Brain regions underlying metabolic regulation and social functioning are rich in OT receptors (Boccia et al., 2013). Thus, to elucidate the role of OT in the central control of metabolism and psychiatric symptoms, it is crucial to determine central OT concentrations. Considering the invasiveness of cerebrospinal fluid (CSF) collection, past research has attempted to approximate central levels by measuring OT in blood plasma or saliva (e.g., Hoge et al., 2008; Rubin et al., 2010). However, peripheral concentrations of OT may not be related to central levels, as central and peripheral OT release can act independently. While research synthesizing the current evidence for the relationship between peripheral and central OT concentrations is currently underway (Valstad et al., 2016), there is still a need to investigate the relationship between central and peripheral OT levels in psychotic disorders (with and without MetS) and healthy controls, along with the association between central OT levels and metabolic factors. In relation to MetS, evidence indicates that peripheral OT levels are reduced in obese and diabetic individuals (Qian et al., 2014). Moreover, peripheral OT levels have been reported to be negatively related to body mass index, waist circumference, fasting glucose, fasting insulin, and triglycerides (Qian et al., 2014). However, other work has reported no difference (Coiro et al., 1988) or increased OT (Stock et al., 1988) in obese individuals, which may reflect the wide variety of sampling method approaches influencing reported levels (Christensen et al., 2014; McCullough et al., 2013). Peripherally administered OT needs to cross the BBB to exert its metabolic effects on central processes. Although only very little peripherally administered OT appears to cross the BBB (Leng and Ludwig, 2016; Mens et al., 1983), others argue that these small amounts can still be physiologically relevant (Neumann et al., 2013).

Alternatively, OT can have indirect effects on CNS processes via the vagal afferent pathway due to peripherally located OT receptors (Quintana et al., 2015a).

6. Repurposing oxytocin for a new indication

The use of psychotropically active therapeutics to alleviate MetS is not a new concept, with two recently approved anti-obesity medications operating via synergistically combining psychotropics with known appetite suppressants using sustained-release formulas: bupropion/naltrexone and phentermine/topiramate (Garvey et al., 2012; Greenway et al., 2010). Intranasal OT is currently approved in a number of territories to assist with breastfeeding via its effects on the milk letdown reflex. Given its known side-effect profile and wide availability, intranasal OT might provide a unique opportunity to investigate an already approved therapeutic for new purposes (Quintana et al., 2016a). However, before OT is trialed in individuals with psychotic disorders, research needs to more clearly characterize the role of the OT system in the etiology of MetS and the potential interacting effects of gender and antipsychotic medications

Like almost any new technology (biomedical or otherwise), biobehavioral OT research is following the so-called ‘hype cycle’ (Alvares et al., 2016b; Mason and Manzotti, 2009), where initial progress leads to overhyped potential, followed by a phase of disillusionment, a period of ‘enlightenment’, then a plateau of productivity when the limits of the new technology are well-characterized. Notwithstanding the dramatic increase in research investigating the biobehavioral effects of OT, there is a dearth of work examining intranasal administration methods (Guastella et al., 2013; Quintana et al., 2016a), understanding how OT exerts its effects on cognition and neural activity by including a control for peripheral effects, and the discovery of the

most efficacious dose (Quintana et al., 2016b; Quintana et al., 2016d). In the same manner as when OT research in the biobehavioral sphere was in its infancy, interest in the potential of OT to address MetS symptoms is rapidly growing (Barengolts, 2016; Blevins and Baskin, 2015; Cai and Purkayastha, 2013; Klockars et al., 2015; Olszewski et al., 2016). Better understanding the mechanisms underlying the role of OT in the development and maintenance of individual MetS risk factors before undertaking a raft of underpowered OT trials (Walum et al., 2016) can accelerate the period of enlightenment for OT and MetS, and if efficacious, a period of research productivity.

Despite the potential of OT to address psychiatric and metabolic symptoms, there are several possible unintended somatic and psychological effects of therapeutic treatment worth considering. OT plays a critical role in multiple physiological systems beyond social and metabolic processes, such as sexual arousal (Argiolas et al., 1986; Melis et al., 2007) bone turnover (Tamma et al., 2009), maternal reflexes (Fuchs et al., 1982; Nishimori et al., 1996), and autonomic nervous system regulation (Kemp et al., 2012; Quintana et al., 2013). A 2011 review of 38 randomized placebo-controlled OT trials including 1529 participants revealed several commonly reported somatic adverse effects, such as light headedness, drowsiness, nasal irritation, dry mouth, and abdominal pain (MacDonald et al., 2011). However, the frequency of these reports did not differ between OT and placebo conditions. This is suggestive of either “nocebo” effects (as the potential for adverse effects are often described in participant information statements provided prior to study enrolment) or the effects of inactive nasal spray ingredients. Although this is encouraging, the quality of adverse events reporting in OT trials is diverse, with only 3 out of 38 trials noting that a medical practitioner was present to assess adverse effects. Moreover, almost 90% of

these trials examined single dose administration, which is less likely than repeated administrations to elicit adverse effects.

Only 132 individuals have completed registered placebo-controlled clinical trials of repeated intranasal OT administration for longer than 4 weeks ($n = 6$ trials; Quintana et al., 2016a), with three of these trials reporting no substantial adverse events (Anagnostou et al., 2012; Guastella et al., 2015; Tachibana et al., 2013). A crossover trial of OT in 31 young children with autism reported that OT was associated with increased thirst, urination, and constipation (Yatawara et al., 2015). There were also three reports of increased aggression and hyperactivity, with two cases occurring during OT treatment. This was consistent with a trial in adolescents and young adults with Prader-Willi syndrome, which reported an increase of temper outbursts in patients receiving a higher dose (32IU or 40IU), but not a lower dose (18IU and 24IU) of OT (Einfeld et al., 2014). Animal development models suggest that repeated OT administrations to adolescent prairie voles (Bales et al., 2013) and neonatal pigs (Rault et al., 2013) may also impair aspects of social behaviour later in life (but see Bales et al., 2014) possibly due to down regulation of OT receptors. While these animal studies underscore the caution required when testing new therapeutics, particularly in children and adolescents, cross-species differences to humans should also be taken into consideration (Young, 2013). There has only been one registered clinical trial of repeated OT dosing in psychotic disorders for four weeks or longer (Cacciotti-Saija et al., 2015). The frequency of adverse events (e.g., thirst, increased or decreased urination, lightheadedness, headache) did not differ between OT and placebo (Cacciotti-Saija et al., 2015), which together with the trial reported by Anagnostou and coworkers (2012) suggests that adults may be less susceptible to adverse OT events than children and adolescents.

In comparison to physical adverse events, unintended psychological effects after single OT administrations are better characterised. Converging research indicates that OT modulates both pro social and non-pro social cognition and behaviours. For instance, a single dose of OT has been shown to increase ethnocentrism (De Dreu et al., 2011), envy, and gloating (Shamay-Tsoory et al., 2009) in neurotypical individuals. In sample of individuals with borderline personality disorder, OT was reported to hinder cooperation for males and females in a social dilemma game (Bartz et al., 2010). These varied behavioural responses to OT highlight the importance of individual differences and context (Bartz et al., 2011). Considering the potential for unintended physiological and psychological effects, any potential benefits of OT on MetS and psychiatric symptoms will need to be weighed up against these risks. Altogether, more research is needed to better characterize the role of the OT system in MetS in psychiatric illness and the circumstances under which exogenous OT exerts its effects.

7. Concluding remarks

Persons suffering from a psychotic disorders have a two to three-fold increased risk of dying from MetS-related diseases, and this mortality has not declined the last few decades (Laursen et al., 2011). This is a major public health issue with a lack of knowledge about clinical characteristics, underlying causes, and effective intervention strategies. Thus, there is an unmet need to better understand the links between MetS and psychotic disorders. While overall population mortality rates are decreasing, the differential mortality in psychotic disorders is increasing (Saha et al., 2007; Schoepf et al., 2014). This differential mortality gap between patients with psychotic disorders and the general population is predicted to continue widening,

which has been primarily attributed to somatic illnesses such as CVD (Crump et al., 2013; Fontaine et al., 2001). Identifying the underlying disease mechanisms of CVD morbidity and mortality in psychotic disorders can lead to major health benefits through the development of new treatments.

In conclusion, early evidence supports the role of OT system dysfunction in both psychotic disorders (Chang et al., 2014; MacDonald and Feifel, 2012; Montag et al., 2013; Tost et al., 2010) and MetS (Blevins and Baskin, 2015; Qian et al., 2014; Yagui et al., 1998). Although more research is clearly needed to understand the contribution of OT system dysfunction to the common co-occurrence of these disorders, manipulation of the oxytocin system has the potential to target underlying mechanisms that may contribute to both MetS and psychotic disorder development. Future OT trials in psychotic disorders assessing behavioural and cognitive outcomes should also include metabolic risk factor parameters.

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Figure 1 caption. A number of cognitive and biological factors are common to psychotic disorders and metabolic Syndrome (MetS), which may be underpinned by oxytocin system dysfunction.

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Table 1. Registered clinical trials investigating the efficacy of intranasal oxytocin to improve metabolic syndrome (MetS) risk factors

Registry	Number	Registration year	Title	Population	MetS outcomes	Status
NIH	NCT01614093	2012	Effects of Intranasal Oxytocin on Satiety Signaling in People With Schizophrenia	Schizophrenia	Satiety signaling, appetite hormone levels	Study complete
NIH	NCT02013258	2013	Oxytocin Trial in Prader-Willi Syndrome	Prader-Willi	Food intake, appetite-regulating hormones	Study complete
NIH	NCT01513499	2012	Effect of Intranasal Oxytocin on Appetite and Caloric Intake in Men and Women	Healthy adults	Caloric intake, appetite, resting energy expenditure	Ongoing
NIH	NCT02629991	2015	Oxytocin vs. Placebo for the Treatment of Hyperphagia in Children and Adolescents With Prader-Willi Syndrome (OXT-PWS)	Prader-Willi	Food intake	Ongoing
NIH	NCT01548521	2011	Tolerance of Intranasal Administration of OT in Prader-Willi Newborn Babies (OTBB)	Prader-Willi (babies)	Food intake	Study complete
NIH	NCT02276677	2014	Oxytocin Effects on Food Motivation Pathways	Healthy adults	Food motivation brain region activity, appetite-regulating hormones	Study complete
NIH	NCT02205034	2014	Evaluation of Tolerance, Suckling and Food Intake After Repeated Nasal Administrations of Oxytocin in PWS Infants (OTBB2)	Prader-Willi (babies)	Food intake, weight gain, appetite-regulating hormones	Study complete
NIH	NCT01038570	2009	Comparative Study Between Prader-Willi Patients Who Take Oxytocin Versus Placebo	Prader-Willi	Food intake	Study complete
EU	2013-004134-15	2013	Intranasal Administration of Oxytocin in Children and Young-Adults with Prader-Willi Syndrome	Prader-Willi	Body composition, food intake	Ongoing
ANZCTR	ACTRN 12609000982213	2009	Oxytocin Treatment for Prader-Willi Syndrome	Prader-Willi	Food intake	Complete

