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The past and future of novel, non-dopamine-2 receptor therapeutics for schizophrenia: A critical and comprehensive review

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ABSTRACT

Since the discovery of chlorpromazine in the 1950's, antipsychotic drugs have been the cornerstone of treatment of schizophrenia, and all attenuate dopamine transmission at the dopamine-2 receptor. Drug development for schizophrenia since that time has led to improvements in side effects and tolerability, and limited improvements in efficacy, with the exception of clozapine. However, the reasons for clozapine's greater efficacy remain unclear, despite the great efforts and resources invested therewith. We performed a comprehensive review of the literature to determine the fate of previously tested, non-dopamine-2 receptor experimental treatments. Overall we included 250 studies in the review from the period 1970 to 2017 including treatments with glutamatergic, serotonergic, cholinergic, neuropeptidergic, hormone-based, dopaminergic, metabolic, vitamin/naturopathic, histaminergic, infection/inflammation-based, and miscellaneous mechanisms. Despite there being several promising targets, such as allosteric modulation of the NMDA and α7 nicotinic receptors, we cannot confidently state that any of the mechanistically novel experimental treatments covered in this review are definitely effective for the treatment of schizophrenia and ready for clinical use. We discuss potential reasons for the relative lack of progress in developing non-dopamine-2 receptor treatments for schizophrenia and provide recommendations for future efforts pursuing novel drug development for schizophrenia.

1. Introduction

Since the serendipitous discovery of chlorpromazine in the 1950's, antipsychotic drugs (APDs) have been the cornerstone of treatment of schizophrenia (Lehmann and Ban, 1997). However, 30% of all schizophrenia subjects do not respond to currently available treatments, and 60% have partial response with residual symptoms persisting (Barbui et al., 2009). Moreover, antipsychotic medications have very limited effects on negative symptoms (Breier et al., 1994; Kasper et al., 2003; Marder et al., 1997; Meltzer et al., 1998; Miyamoto et al., 2005) and cognitive deficits (e.g., working memory, verbal memory, attention, executive functioning) (Davidson et al., 2009; Green et al., 1997, 2002; Keefe et al., 1999, 2004, 2006, 2007; Kern et al., 1998; Miyamoto et al., 2005), and no medications are currently approved for the treatment of residual psychotic, negative or cognitive symptoms. In addition, metabolic disturbances such as hyperglycemia, hyperlipidemia, obesity and diabetes can add to the morbidity of schizophrenia and decrease patient adherence to the required long-term treatment regimens (Marder et al., 2004). New therapies are needed that provide rapid improvement in active psychotic symptomatology, negative symptoms, and cognitive deficits, along with better tolerability. However, there has been relatively little progress in the development of new treatments since the introduction of antipsychotic medications.

First generation APDs had high affinity and were full antagonists at D-2 receptors, while second generation APDs were D-2 receptor antagonists and possessed higher affinity for other neuro-receptors including the 5-HT2A receptors (Miyamoto et al., 2012). More recently, compounds have been developed that represent variations on this D-2 receptor super-family and include partial agonists at the D-2 receptor (aripiprazole and brexpiprazole), D-3 selective compounds (cariprazine [Allergan] and F1764 [Pierre Fabre]) and ITI-007 (Intracellular Therapies) which acts intra and extracellularly and at multiple neuroreceptors including D-2 (Lieberman et al., 2016; Durgam et al., 2014; Rakhit et al., 2014).

Landmark comparative effectiveness studies such as CATIE, CUTLASS, and EUFEST showed that older and newer medications were more similar than different (with the greatest exception being clozapine), with the greatest differences being in side effects (Jones et al., 2006; Kahn et al., 2008; Lieberman et al., 2005). Clozapine is unique in that it is an effective antipsychotic medication and exhibits therapeutic

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Table 1
Clinical trials of experimental medications with glutamatergic mechanisms.

Name (Mechanism)	Reference	Design	Sample	Length	Treatment Conditions	Primary Outcome	Results	Comment
Sarcosine (Glycine transporter-1 inhibitor) and Sodium Benzoate (D-amino acid oxidase)	(Lin et al., 2017b)	RCT, Add-on, Double Blind	63	12 weeks	Sarcosine 2 g/day + Benzoate 1 g/day, Sarcosine 2 g/day, Placebo	PANSS total, global and neurocognitive composite of Chinese MCCB equivalent	Improvement in global and neurocognitive composite scores in Sarcosine + Benzoate over both Sarcosine and placebo groups, no difference in PANSS total	Taiwanese inpatients, required PANSS > 60, small sample
Sarcosine (Glycine transporter-1 inhibitor) and D-Serine	(Lane et al., 2010)	RCT, Add-on, Double Blind	60	6 weeks	Sarcosine 2 g/day, D-Serine 2 g/day, Placebo	PANSS, SANS, QOL, GAF	Improvement with Sarcosine on PANSS total, SANS, QOL, and GAF, no differences for D-serine	Han Chinese inpatients
Sarcosine (Glycine transporter-1 inhibitor)	(Lane et al., 2008)	RCT, Add-on, Double Blind	20	6 weeks	Sarcosine 1 g/day, Sarcosine 2 g/day	PANSS, SANS, QOL	No differences	Acutely ill Han Chinese inpatients
Sarcosine (Glycine transporter-1 inhibitor)	(Lane et al., 2006)	RCT, Add-on, Double Blind	20	6 weeks	Sarcosine 2 g/day, Placebo	PANSS	No differences	Add-on to clozapine, hypothesized negative result
Sarcosine (Glycine transporter-1 inhibitor) and D-Serine	(Lane et al., 2005)	RCT, Add-on, Double Blind	65	6 weeks	Sarcosine 2 g/day, D-Serine 2 g/day, Placebo	PANSS, SANS	Sarcosine superior to D-Serine and Placebo on PANSS total, general, cognitive, depressive, SANS	Add on to risperidone
Sarcosine (Glycine transporter-1 inhibitor)	(Tsai et al., 2004)	RCT, Add-on, Double Blind	38	6 weeks	Sarcosine 2 g/day, Placebo	PANSS, SANS, BPRS	Improvement on BPRS, SANS, and PANSS positive, cognitive, general, and total	Add on to non-clozapine antipsychotics
Bitopertin (Glycine transporter-1 inhibitor)	(Bugarski-Kirola et al., 2014a,b)	RCT, Monotherapy, Double Blind	301	4 weeks	Bitopertin 10 mg/day, Bitopertin 30 mg/day, Olanzapine 15 mg/day, Placebo	PANSS	No differences	Failed active comparator, multicenter phase II/III trial, used LOCF
Bitopertin (Glycine transporter-1 inhibitor)	(Arango et al., 2014)	RCT, Add-on, Double Blind	605	24 weeks	Bitopertin 5 mg/day, Bitopertin 10 mg/day, Placebo	PANSS negative symptoms factor score	No differences	Multicenter phase III DayLyte study, stable patients
Bitopertin (Glycine transporter-1 inhibitor)	(Umbricht et al., 2014a)	RCT, Add-on, Double Blind	323	8 weeks	Bitopertin 10 mg/day, 30 mg/day, 60 mg/day, Placebo	PANSS	Improvement in PANSS negative symptoms at 10 mg/day and 30 mg/day, no differences at 60 mg/day	Phase II multicenter trial
Bitopertin (Glycine transporter-1 inhibitor)	(Blaettler et al., 2014)	RCT, Add-on, Double Blind	627	24 weeks	Bitopertin 10 mg/day, Bitopertin 20 mg/day, Placebo	PANSS negative symptoms factor score	No differences	Multicenter phase III FlashLyte study, stable patients, used ITT
Sodium Benzoate (D-amino acid oxidase inhibitor)	(Lin et al., 2017a)	RCT, Add-on, Double Blind	60	6 weeks	Sodium Benzoate 1 g/day, 2 g/day, Placebo	PANSS Total, SANS-20, QOL, GAF	Improvement on SANS-20 for both doses, QOL and PANSS total for 2 g dose, no difference in GAF for either dose	Taiwanese inpatients, resistant to clozapine, PANSS > 70, SANS > 40, change in catalase correlated with improvement in PANSS total/positive scores
Sodium Benzoate (D-amino acid oxidase inhibitor)	(Lane et al., 2013)	RCT, Add-on, Double Blind	52	6 weeks	Sodium Benzoate 1 g/day, Placebo	PANSS Total	Improvement on PANSS total, negative, general, positive, SANS, CGI, GAF, QOLS, processing speed, visual learning memory, MCCB composite score	Taiwanese outpatients, required PANSS > 60, large effect sizes
LY2140023 (mGlu 2/3 receptor agonist)	(Kinon et al., 2011)	RCT, Monotherapy, Double Blind	667	4 weeks	LY2140023 5 mg, 20 mg, 40 mg, or 80 mg BID, Olanzapine 15 mg/day, Placebo	PANSS total	No differences	Failed active comparator, multicenter phase II trial, four seizures in treatment group,
LY2140023 (mGlu 2/3 receptor agonist)	(Patil et al., 2007)	RCT, Monotherapy, Double Blind	196	4 weeks	LY2140023 40 mg BID, Olanzapine 15 mg/day, Placebo	PANSS total	Improvement on total, negative, and positive subscales	Active comparator, multicenter trial, placebo group worsened significantly
Sodium Nitroprusside (NMDA receptor modulator)	(Hallak et al., 2013)	RCT, Add-on, Double Blind	20	Single dose, monitored for 4 weeks	One-time dose of IV Nitroprusside 0.5 μg/kg/min for 4 h, Placebo	PANSS negative subscale and BPRS	Improvement within 4 h on BPRS and PANSS negative subscale, effect persisted for 4 weeks	Single dose study, unknown validity of scales for rapid serial assessments

(*continued on next page*)

Table 1 (*continued*)

Name (Mechanism)	Reference	Design	Sample	Length	Treatment Conditions	Primary Outcome	Results	Comment
D-Cycloserine	(Cain et al., 2014)	RCT, Add-on, Double Blind	36	8 weeks	DCS 50 mg q 1 week, Placebo	MCCB composite, SANS total, auditory discrimination task (ADT)	DCS superior to placebo on SANS (for patients with SANS > 20), and ADT, placebo outperformed DCS on MCCB composite	Cognitive remediation for ADT placebo group did not improve
D-Cycloserine	(Gottlieb et al., 2011)	Crossover, Add-on, Double Blind	21	2 visits, 1 week apart	DCS 50 mg single dose 1 h prior to CBT training, Placebo	SAPS global delusions score	No differences	Stable outpatients, order effect of first visit
D-Cycloserine	(Goff et al., 2008a)	RCT, Add-on, Double Blind	38	8 weeks	DCS 50 mg/day q 1 week, Placebo	SANS total, Composite Cognitive Score	Improvement on SANS, otherwise no differences	Negative symptoms worsened in placebo group
D-Cycloserine	(Goff et al., 2005)	RCT, Add-on, Double Blind	55	6 months	DCS 50 mg/day, Placebo	SANS total score	No differences	Prominent negative symptoms, 47% drop out, LOCF used
D-Cycloserine	(Duncan et al., 2004)	RCT, Add-on, Double Blind	22	4 weeks	DCS 50 mg/day, Placebo	BPRS, SANS, Abrams and Taylor	No differences	Required SANS > 30 and deficit syndrome
D-Cycloserine	(Evins et al., 2002)	RCT, Add-on, Single Blind	10	2 weeks	DCS 5 mg/day, 10 mg/day, 50 mg/day, 250 mg/day (each patient took 4 doses), Placebo	SANS	Improvement on SANS at 50 mg/day, no differences otherwise	Required SANS > 30 and deficit syndrome, add-on to risperidone, single blind
D-Cycloserine	(Heresco-Levy et al., 2002)	Add-on, Crossover	24	14 weeks total (2 week wash out)	DCS 50 mg/day, Placebo	PANSS	Improvement on PANSS negative and total, no differences otherwise	Evaluated differences in first vs. second generation antipsychotics
D-Cycloserine	(van Berckel et al., 1999)	RCT, Add-on, Double Blind	26	8 weeks	DCS 50 mg BID, Placebo	PANSS	Worsening on PANSS positive, general, and total subscales, no difference otherwise	Required moderate severity on two PANSS negative items
D-Cycloserine	(Goff et al., 1999b)	RCT, Add-on, Double Blind	47	8 weeks	DCS 50 mg/day, Placebo	SANS	Improvement on SANS, no difference otherwise	Add-on to typical antipsychotics
D-Cycloserine	(Goff et al., 1999a)	Crossover, Add-on, Double Blind	17	13 weeks (1-week washout)	DCS 50 mg/day, Placebo	SANS, PANSS	Worsened negative symptoms, no difference otherwise	Add-on to clozapine, required SANS > 30, outpatients
D-Cycloserine	(Rosse et al., 1996)	RCT, Add-on, Double Blind	13	4 weeks	DCS 5 mg BID + Molindone 50 mg TID, 15 mg BID + Molindone 50 mg TID, Placebo + Molindone 50 mg TID	BPRS, SANS, CGI	No differences	Add-on to molindone, acutely ill inpatients, required BPRS ≥ 35, low dose of DCS
D-Cycloserine	(Goff et al., 1995)	Crossover, Add-on, Double Blind	9	8 weeks (2 weeks of each arm, no washout)	DCS 5 mg/day, 15 mg/day, 50 mg/day, 250 mg/day, Placebo	BPRS, SANS, GAS, Sternberg's Item Recognition Paradigm (SIRP)	DCS 50 mg/day only associated with improvement in SANS, BPRS negative subscale, reaction time on SIRP	Non-blind interviewers
Glycine	(Woods et al., 2013)	RCT, Monotherapy, Double Blind	8	12 weeks	Glycine 0.4 g/kg BID (or 80 g/d if weighing > 100 kg), Placebo	SOPS	Improvement in SOPS positive, negative, disorganized, and total in the RCT	Prodromal patients, two trials (first open label, second RDB converted to open)
Glycine and D-Cycloserine	(Buchanan et al., 2007)	RCT, Add-on, Double Blind	157	16 weeks	Glycine 60 g/day + placebo, DCS 50 mg/day + placebo, Placebo + placebo	SANS total rate of change over time and change in average cognitive domain z scores	DCS improvement in SANS total score (only one site), otherwise no differences	Multicenter, inpatients and outpatients, site effects
Glycine	(Diaz et al., 2005)	Crossover, Add-on, Double Blind	12	28 weeks	Glycine 60 g/day, Placebo	PANSS total, negative, positive, BPRS, GAF	No differences	Add-on to clozapine
Glycine	(Heresco-Levy et al., 2004)	Crossover, Add-on, Double Blind	17	6 weeks	Glycine 0.8 g/kg/day, Placebo	PANSS, BPRS	Improvement greatest in PANSS negative, cognitive subscales (modest effect for others) and BPRS total	Add-on to olanzapine and risperidone, chronic inpatients, used LOCF
Glycine	(Javitt et al., 2001)	Crossover, Add-on, Double Blind	12	14 weeks total (2 week wash out)	Glycine 0.8 g/kg/day TID dosing, Placebo	PANSS	Improvement in negative subscale, no differences otherwise	Four subjects taking clozapine did not worsen
Glycine	(Evins et al., 2000)	RCT, Add-on, Double Blind	30	8 weeks	Glycine 60 g/day, Placebo	SANS, PANSS, BPRS, GAF	No differences, no worsening of positive symptoms	Add-on to clozapine, outpatients, used LOCF

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Table 1 (*continued*)

Name (Mechanism)	Reference	Design	Sample	Length	Treatment Conditions	Primary Outcome	Results	Comment
Glycine	(Heresco-Levy et al., 1999)	Crossover, Add-on, Double Blind	22	14 weeks (2 week wash out)	Glycine 0.8 g/kg/day TID dosing, Placebo	PANSS, BPRS	Improvement in PANSS negative and BPRS total scores	Low serum glycine levels predicted response
Glycine	(Potkin et al., 1999)	RCT, Add-on, Double Blind	19	12 weeks	Glycine 30 g/day, Placebo	SANS, BPRS	Placebo superior to glycine on BPRS total, no differences otherwise	Add-on to clozapine
BL-1020 (D2 blocker + GABA-a agonist)	(Geffen et al., 2012)	RCT, Monotherapy, Double Blind	363	6 weeks	BL-1020 10 mg/day, BL-1020 20–30 mg/day, Risperidone 2–8 mg/day, Placebo	PANSS total, BACS	Improvement in PANSS total with BL-1020 20–30 mg and Risperidone 2–8 mg, only BL-1020 20–30 mg improved BACS composite score	Moderately ill inpatients, used LOCF and intent to treat
Muscimol (GABA-a agonist)	(Tamminga et al., 1978)	Monotherapy, Double Blind	6	Unknown	Muscimol 7–10 mg, Placebo	Semi-structured clinical interview	Worsening of psychosis compared to placebo	No randomization
Lorazepam (GABA-a agonist) and Flumazenil (GABA-a antagonist/inverse agonist)	(Menzies et al., 2007)	Crossover, Add-on, Double Blind	11 SCZ, 11 healthy control	2 weeks	Lorazepam 2 mg, Flumazenil 0.9 mg then 0.0102 mg/min (dosed once per visit, 3 visits), Placebo	Working memory via N-Back task	Lorazepam impaired performance on N-Back task in both SCZ/Controls, but more so in SCZ and with harder tasks, flumazenil slightly improved performance on N-back compared to placebo	Not a clinical trial, controls did not have SCZ
D-Serine	(D'Souza et al., 2013)	RCT, Add-on, Double Blind	104	12 weeks	D-Serine 30 mg/kg/day + Cognitive retraining (CRT), D-serine 30 mg/kg/day + control CRT, CRT + placebo, control CRT + placebo	Feasibility, safety, and tolerability of multisite trial, PANSS, Cognitive Battery	Improvement in CRT group on Verbal Working Memory, no differences otherwise	Add-on to cognitive retraining, multicenter feasibility trial, used LOCF, site differences in baseline symptoms and cognitive function
D-Serine	(Weiser et al., 2012b)	RCT, Add-on, Double Blind	195	16 weeks	D-Serine 2 g/day, Placebo	SANS and MCCB	No differences	Multicenter study, fixed dosing, used LOCF
D-Serine	(Heresco-Levy et al., 2005)	Crossover, Add-on, Double Blind	39	15 weeks (3 week wash out)	D-Serine 30 mg/kg/day, Placebo	PANSS, BPRS, SANS	Improvement in SANS, BPRS total, all PANSS subscales	Order effect noted, inpatients
D-Serine	(Tsai et al., 1999)	RCT, Add-on, Double Blind	20	6 weeks	D-Serine 30 mg/kg/day, Placebo	PANSS positive, cognitive, and general subscales, SANS, CGI, WCST	No differences	Add-on to clozapine, treatment-resistant, deficit syndrome inpatients
D-Serine	(Tsai et al., 1998)	RCT, Add-on, Double Blind	31	6 weeks	D-Serine 30 mg/kg/day, Placebo	PANSS positive, general, and cognitive subscales, SANS, CGI, WCST	Improvement in PANSS positive and cognitive subscales, SANS, WCST category score, CGI, no differences otherwise	Treatment-resistant, deficit syndrome inpatients and day program patients in Taiwan
D-Alanine	(Tsai et al., 2006)	RCT, Add on, Double Blind	32	6 weeks	100 mg/kg/day D-alanine, Placebo	PANSS, SANS, HDRS	Improvement on PANSS total, positive, and cognitive, CGI, SANS	Treatment resistant patients
Diazoxide (K+ channel opener and positive allosteric modulator of AMPA/kainite receptors)	(Akhondzadeh et al., 2002)	RCT, Add-on, Double Blind	46	8 weeks	Diazoxide 200 mg/day + haloperidol 20 mg/day, haloperidol 20 mg/day + Placebo	PANSS	Improvement on PANSS positive subscale only	Add-on to haloperidol, inpatients, required minimum total PANSS score of 60
CX516 (Ampakine –binds AMPA receptor allosteric site)	(Goff et al., 2008b)	RCT, Add-on, Double Blind	105	4 weeks	CX516 900 mg TID, Placebo	Cognitive battery	No differences	Multicenter study, stable outpatients, used ITT
CX516 (Ampakine –binds AMPA receptor allosteric site)	(Goff et al., 2001)	RCT, Add-on, Double Blind	19	4 weeks	CX516 900 mg TID, Placebo	PANSS, SANS, HAM-D, GAS, Cognitive battery	Improvement in SANS attention item, HAM-D, PANSS total and negative, GAS, GDS, Distraction Test, Rey-Osterrieth and Taylor Complex Figure Tests, and Trails B (Time)	Add-on to clozapine, significant group differences at baseline (CX516 group more cognitively impaired)

(*continued on next page*)

Table 1 (*continued*)

Name (Mechanism)	Reference	Design	Sample	Length	Treatment Conditions	Primary Outcome	Results	Comment
Acamprosate (reportedly NMDA receptor partial agonist, mGluR antagonist though largely unknown)	(Ralevski et al., 2011)	RCT, Add-on, Double Blind	23	12 weeks	Acamprosate 1998 mg/day, Placebo	PANSS, Cognitive battery	No difference on any measures	Goal was to demonstrate absence of cognitive worsening with acamprosate
L-Theanine (neuroprotection of NMDA receptor mediated neurotoxicity)	(Ritsner et al., 2011)	RCT, Add-on, Double Blind	60	8 weeks	L-theanine 200 mg BID, Placebo	PANSS, Hamilton Anxiety Rating Scale (HARS), CANTAB, CGI	Improvement in HARS, PANSS positive and activation factor after Bonferroni correction, no differences otherwise	Two-site study, inpatients and outpatients in Israel, used LOCF
Riluzole (neuroprotection of NMDA receptor mediated neurotoxicity)	(Farokhnia et al., 2014)	RCT, Add-on, Double Blind	50	8 weeks	Riluzole 100 mg/day, Placebo	PANSS negative subscale	Riluzole superior to placebo on PANSS negative, total, and general subscales, no difference for PANSS positive symptoms	All patients switched to Risperdal, Minimum PANSS of 60 and > 20 on negative subscale
Minocycline (neuroprotection against NMDA receptor induced neurotoxicity)	(Kelly et al., 2015)	RCT, Add-on, Double Blind	52	10 weeks	Minocycline 100 mg BID, Placebo	MATRICS Consensus Cognitive Battery (MCCB), BPRS, SANS	Improvement in SANS avolition and BPRS anxiety/depression factor, no differences otherwise	Add-on to clozapine, outpatients, multicenter
Minocycline (neuroprotection against NMDA receptor induced neurotoxicity)	(Liu et al., 2014)	RCT, Add-on, Double Blind	92	16-week	Minocycline 200 mg/day, Placebo	SANS, PANSS, CGI-S, MATRICS Consensus Cognitive Battery (MCCB)	Improvement in SANS total, PANSS total, negative, general, CGI-S, no differences otherwise	
Minocycline (neuroprotection against NMDA receptor induced neurotoxicity)	(Khodaie-Ardakani et al., 2014)	RCT, Add-on, Double Blind	40	8 weeks	Minocycline 200 mg/day, Placebo	PANSS, HDRS	Superior to placebo on PANSS negative, total, and general subscales, no difference in PANSS positive and HDRS	LOCF for 2 patients who dropped out of placebo group
Minocycline (neuroprotection against NMDA receptor induced neurotoxicity)	(Chaudhry et al., 2012)	RCT, Add-on, Double Blind	144	1 year	Minocycline 200 mg/day, Placebo	PANSS	Improvement on PANSS negative, no differences otherwise	Multicenter trial, treatment-by-country interaction
Minocycline (neuroprotection against NMDA receptor induced neurotoxicity)	(Levkovitz et al., 2010)	RCT, Add-on, Double Blind	54	24 weeks	Minocycline 200 mg/day, Placebo	SANS, CANTAB	Improvement in SANS and CANTAB	
Memantine (neuroprotection against NMDA receptor induced neurotoxicity)	(Veerman et al., 2016)	Crossover, Add-on, Double Blind	52	26 weeks (2 week wash out)	Memantine 20 mg/day, Placebo	CANTAB (memory and executive function were primary), PANSS, CGI	Improvement in CANTAB memory composite and PANSS negative subscale, no differences otherwise	Add-on to clozapine, noted carryover effects on verbal memory, PANSS
Memantine (neuroprotection against NMDA receptor induced neurotoxicity)	(Omranifard et al., 2015)	RCT, Add-on, Double Blind	64	12 weeks	Memantine 20 mg/day, Placebo	GAF, QLS	Improvement in GAF and QLS	Add-on to atypical antipsychotics, Iranian inpatients
Memantine (neuroprotection against NMDA receptor induced neurotoxicity)	(Rezaei et al., 2013)	RCT, Add-on, Double Blind	40	8 weeks	Memantine 20 mg/day (week 1, 10 mg/day; week 2–8, 20 mg/day), Placebo	PANSS	Memantine superior to placebo on PANSS total, negative subscale, and general psychopathology, no difference on PANSS positive subscale	Add-on to risperidone, LOCF used for 2 dropouts
Memantine (neuroprotection against NMDA receptor induced neurotoxicity)	(de Lucena et al., 2009)	RCT, Add-on, Double Blind	21	12 weeks	Memantine 20 mg/day, Placebo	BPRS total, positive, and negative subscales	Improvement in BPRS total, negative, and positive subscales	Add-on to clozapine, treatment-resistant outpatients
Memantine (neuroprotection against NMDA receptor induced neurotoxicity)	(Lieberman et al., 2009)	RCT, Add-on, Double Blind	138	8 weeks	Memantine 20 mg/day, Placebo	PANSS total	No differences	Multicenter trial, non-clozapine antipsychotics, used LOCF

efficacy in some proportion of patients who do not respond to other antipsychotic medications (Kane et al., 1988). Although clozapine's side effect profile (agranulocytosis, myocarditis, sialorrhea, weight gain, seizures) limits its use, there are available treatments to reduce the cardiometabolic side effects such as metformin (Siskind et al., 2016) and fluvoxamine (Lu et al., 2004).

Recent antipsychotic drug development has aimed at new molecular targets other than the D-2 receptor including D-1, D-4, D-3, NMDA, 5-HT2A, 5-HT2C, M-1,4, H-3, NK-3, and sigma receptors (Karam et al., 2010; Miyamoto et al., 2012). However, thus far, no compound that does not possess at least a modicum of affinity for the D-2 receptor and the ability to attenuate (if not block) neurotransmission by the endogenous ligand DA has been proven to be effective for any symptom dimension of schizophrenia. Further, while agents that target the D-2 receptor are effective in treating positive symptoms, no compound/target has proven to be reliably effective in the treatment of cognitive or negative symptoms. To address these two major problems, in 2003, a neuropsychopharmacology advisory group working under the auspices of the NIMH and FDA developed a list of prioritized targets for drug development for cognitive impairment in schizophrenia (MATRICS) (Marder, 2006; Tamminga, 2006). Enormous effort and resources have been invested by academia, industry, public/governmental institutions, and private/philanthropic organizations to develop and test compounds active at a number of these targets. However, the results have not been fruitful, because either the target, the compound, or the way it was tested failed. Thus, it is imperative to identify alternative strategies for novel drug development that should be pursued and review what have we learned from prior experience to inform future efforts so they will be more successful (Karam et al., 2010).

To address this question, we carried out a comprehensive review of the literature to determine the fate of previously tested experimental, non-D-2 receptor, treatments. We searched the PubMed database using the following search terms: "(schizophrenia or schizoaffective or schizophreniform) and (clinical trial or proof of concept or proof-of-concept)" [initial search performed on 4/3/16]. We also substituted "proof of principle" for "proof of concept." We also reviewed the bibliographies of the chosen articles and included any studies that were not included in our search. We focused our review on the clinical trials with efficacy outcomes related to positive, negative, and cognitive symptoms, as opposed to clinical trials aimed at decreasing side effects, other non-specific symptoms such as insomnia, or comorbid conditions (e.g., alcohol or tobacco use). So, for example, while numerous trials have been performed with naltrexone/naloxone, we only report on efficacy outcomes and trials. In addition, we did not include trials of antidepressants, anti-epileptics (e.g., lamotrigine, gabapentin, etc.), other mood stabilizers (lithium, valproic acid), beta blockers, amphetamine-based stimulants, benzodiazepines, barbiturates, and other hypnotics and similar medications (e.g., zolpidem, baclofen, fenfluramine). We did not include trials of agents that are primarily D-2 receptor antagonists, did not include open label trials and did not report on trials with only biomarker outcomes. Finally, we did not include the majority of single dose trials or trials with extremely small sample sizes (e.g, less than 10). Prior studies were examined specifically for; 1) Why did treatments/targets fail (e.g., methodology, target, pharmacology); 2) Is further study of these compounds/targets warranted; 3) What are the implications of this body of resarch for future drug discovery.

Overall we included 250 studies in the review from the period 1970 to 2017 (initial search performed on 4/3/16). They are organized in the following categories: glutamatergic, serotonergic, cholinergic, neuropeptides, hormones, dopaminergic, metabolic, vitamins/naturopathic, histaminergic, infection/inflammation, and miscellaneous, with a table corresponding to the narrative commentary for each.

2. Glutamatergic medications

Beginning with the seminal paper by Javitt and Zukin (1991), hypofunction of N-methyl-D-aspartate (NMDAR) type glutamate receptors has been hypothesized to play a central role in the pathophysiology of schizophrenia (Coyle, 2012; Javitt and Zukin, 1991; Moghaddam and Krystal, 2012). Due to the toxicity of NMDAR agonists working through the glutamate site, strategies for pharmacologic enhancement of NMDA receptor-mediated neurotransmission have been pursued through alternative mechanisms.

Co-agonism of the glycine binding site of the NMDA receptor with glycine, D-serine, D-cycloserine, or D-alanine is one method for enhancing glutamatergic neurotransmission (Table 1). Trials of D-serine and glycine have been mixed with positive results in early small trials and negative results in a more recent large, multicenter trial and in trials when added to clozapine (Buchanan et al., 2007; D'Souza et al., 2013; Diaz et al., 2005; Evins et al., 2000; Heresco-Levy et al., 2004; Heresco-Levy et al., 2005; Heresco-Levy et al., 1999; Javitt et al., 2002; Potkin et al., 1999; Tsai et al., 1998; Tsai et al., 2006; Tsai et al., 1999; Weiser et al., 2012b). D-serine has recently been shown to reduce negative symptoms in individuals at symptomatic clinical high risk (CHR) for schizophrenia (Kantrowitz et al., 2015), in association with reduction in inflammatory biomarkers.

D-cycloserine is a partial agonist, with net potentiating effects on NMDAR-mediated neurotransmission only at doses < 100 mg. Trials with D-cycloserine have largely been negative overall with small trials showing some benefit for negative symptoms in patients taking non-clozapine antipsychotics, but worsening negative symptoms when added to clozapine (Cain et al., 2014; Duncan et al., 2004; Goff et al., 1999a, 1999b, 2005, 2008a; Gottlieb et al., 2011; Heresco-Levy et al., 2002), or worsening positive symptoms at 100 mg (Table 1) (van Berckel et al., 1999). This may be because D-cycloserine is a partial agonist of the glycine binding site and acts as an agonist at low doses, but as an antagonist at higher doses (Emmett et al., 1991).

Another method of increasing glycine concentration at the glycine binding site is inhibition of the glycine transporter. Sarcosine (N-methylglycine) is a naturally occurring glycine transporter inhibitor that works at both glycine type 1 (GlyT1) and "System A" type glycine transporters (Javitt et al., 2005). Several initial trials of sarcosine were positive (Lane et al., 2005, 2008, 2010; Tsai et al., 2004), but a more recent trial of sarcosine showed no improvement in PANSS or cognitive function when used alone (Lin et al., 2017b). Additionally, there was no improvement in the PANSS score when added to clozapine, as has been noted with other glutamatergic medications (Lane et al., 2006).

Bitopertin, a high affinity GlyT1 inhibitor, initially demonstrated significant improvement of negative symptoms in a phase II multicenter trial of patients with significant negative symptoms, though only among completers who finished all study procedures (Umbricht et al., 2014a). Subsequent trials with bitopertin, Org 25935, and AMG-747 were either mixed or negative on most primary outcomes (Table 1) (Blaettler et al., 2014; Bugarski-Kirola et al., 2014a,b; Dunayevich et al., 2017). Importantly, however, a very narrow therapeutic window was observed for these agents.

Positive allosteric modulation of group II metabotropic glutamate receptors (mGluR2/3), which are typically located on presynaptic terminals and inhibit neurotransmitter release and modulate neurotransmission via G protein coupled second messenger systems, provides an alternative mechanism to co-agonism of the ionotropic NMDA receptor (Niswender and Conn, 2010). The initial phase II multicenter trial of LY2140023 (pomaglumetad), demonstrated dramatic improvement compared to placebo on PANSS total, negative, and positive subscales, with efficacy nearly equal to olanzapine but with a much improved safety profile including significant reduction in body weight and lack of an effect on prolactin levels (Patil et al., 2007). Follow up studies were equivocal or clearly negative (Downing et al., 2014; Kinon et al., 2011; Stauffer et al., 2013), though post-hoc analysis suggests that pomaglumetad may be specifically effective in individuals with duration of illness ≤3 yrs, especially those without prior exposure to antipsychotic (Kinon et al., 2015), potentially related to higher basal

brain glutamate levels observed in this population (Marsman et al., 2013). Another concern regarding pomaglumetad development is that in vivo target engagement was not verified at the doses used. Future studies in early stage populations and using higher dose of medication may therefore be warranted.

Ampakines bind to an allosteric site of the AMPA receptor and prolong AMPA receptor depolarization, triggering removal of the magnesium block from NMDA receptor ion channels. A small trial of CX516, an ampakine, showed improvement in measures of memory and attention (Goff et al., 2001), however, a larger follow up trial was negative (Goff et al., 2008b). Individual trials of piracetam, a compound that stimulates the AMPA receptor and has a number of additional effects in the brain, and diazoxide, a positive allosteric modular of AMPA/kainate receptors, were also preliminarily positive, but require replication (Akhondzadeh et al., 2002; Noorbala et al., 1999).

Minocycline, a tetracycline antibiotic, has broad effects on several pathways implicated in schizophrenia including reducing glutamatergic excitotoxicity and enhancing GluR1 AMPA receptor subtypes in addition to anti-oxidant, anti-inflammatory, neurotrophic, and anti-apoptotic properties (Dean et al., 2012; Wang et al., 2005). Trials of minocycline have been mixed and demonstrated improvement in selective symptom domains (Table 1) (Chaudhry et al., 2012; Kelly et al., 2015; Khodaie-Ardakani et al., 2014; Levkovitz et al., 2010; Liu et al., 2014). Memantine, a low-affinity antagonist at the NMDA receptor, has also been hypothesized to have protective effects against NMDA receptor-mediated neurotoxicity and anti-inflammatory properties (Wu et al., 2009). Memantine trials have also demonstrated mixed results (de Lucena et al., 2009; Lieberman et al., 2009; Omranifard et al., 2015; Rezaei et al., 2013; Veerman et al., 2016). There have been three trials of sodium benzoate, a D-amino acid oxidase inhibitor, including one trial in clozapine-resistant patients (Lin et al., 2017a), that have shown improvement on composite cognitive measures and variable improvement in PANSS and SANS scores (Lane et al., 2013; Lin et al., 2017b). While the improvement in cognitive function in two trials is encouraging, the mixed results with respect to positive and negative symptoms necessitates larger trials of sodium benzoate to clarify its effects. Individual trials of riluzole, a neuroprotective glutamate modulating agent (Farokhnia et al., 2014), and L-theanine, a neuroprotective NMDA and AMPA receptor antagonist (Ritsner et al., 2011), were positive, but were small studies and have yet to be replicated.

3. Serotonergic medications

The serotonin (5-HT) neurotransmitter system has been hypothesized to play a role in the pathophysiology of schizophrenia. Activation of the 5-HT2A receptor by agonists such lysergic acid diethylamide (LSD) produces hallucinatory experiences (Glennon et al., 1984), suggesting a possible role for 5-HT2A antagonists as anti-psychotic medications. Additionally, 5-HT2C receptor agonism has been shown to tonically suppress mesocortical, mesolimbic, and nigrostrial dopaminergic pathways (Gobert et al., 2000).

A number of trials have been performed with agents that target these receptors such as ritanserin, a 5-HT2A/2C antagonist (Akhondzadeh et al., 2008b; Den Boer et al., 2000), SR46349B, also a 5HT2A/2C antagonist (Meltzer et al., 2004), vabicarserin, a 5-HT2C agonist, pimavanserin, a 5-HT2A inverse agonist (Meltzer et al., 2012), fananserin, a 5-HT2A and D4 antagonist (Truffinet et al., 1999), mianserin, a 5-HT2A/2B/2C and α2 adrenergic antagonist (Shiloh et al., 2002), and dimebon, a 5-HT6 antagonist (Table 2) (Morozova et al., 2012). These trials have yielded mixed results.

Antagonists of the 5-HT3 receptor, which has been shown to modulate neurotransmitter release in mesocortical and mesolimbic dopamine neurons (Hagan et al., 1993), include medications such as ondansetron, tropisetron, and granisetron. Two trials of ondansetron, one study of granisetron, and one study of tropisetron demonstrated improvement in PANSS negative and total symptoms (Akhondzadeh et al., 2009; Khodaie-Ardakani et al., 2013; Noroozian et al., 2013; Zhang et al., 2006). Another study of tropisetron found no difference in PANSS or CANTAB scores (Shiina et al., 2010), but noted an improvement in auditory sensory gating P50 deficits along with a subsequent trial examining P50 deficits (Zhang et al., 2012). A brief, small trial of L-tryptophan, the amino acid precursor to serotonin, was associated with better performance on several cognitive measures, but no improvement in symptoms on the PANSS (Table 2) (Levkovitz et al., 2003). A very recent trial of monotherapy with MIN-101, a sigma 2 and 5-HT2A antagonist, reported improvements in negative symptoms after 12 weeks of treatment, though these improvements may have been related to treatment of extrapyramidal symptoms as subjects had been off oral APDS for only three days before beginning the study drug (Davidson et al., 2017).

4. Cholinergic medications

The nicotinic cholinergic neurotransmitter system has been implicated in the pathophysiology of schizophrenia. Genetic studies have shown associations between several nicotinic receptor genes (*CHRNA3, CHRNA5, CHRNA7, CHRNB4)* and an increased risk of developing schizophrenia (Leonard et al., 2002; Schizophrenia Working Group of the Psychiatric Genomics, 2014). Additionally, postmortem studies have shown that individuals with schizophrenia have reduced expression of the hippocampal nicotinic receptors (Freedman et al., 1995). Nearly all trials of acetylcholinesterase inhibitors including donepezil, galantamine, and rivastigmine targeting negative and cognitive symptoms were negative (Table 3) (Akhondzadeh et al., 2008a; Buchanan et al., 2008; Dyer et al., 2008; Erickson et al., 2005; Fagerlund et al., 2007; Freudenreich et al., 2005; Friedman et al., 2002; Keefe et al., 2008; Kohler et al., 2007; Lee, et al., 2007a; Lindenmayer and Khan, 2011; Mazeh et al., 2006; Sacco et al., 2008; Stryjer et al., 2004; Tugal et al., 2004).

Trials of varenicline, an α7 nicotinic receptor agonist and α4β2 partial agonist, showed improvements in certain endophenotypic measures (Hong et al., 2011), reduced urges to smoke and number of cigarettes (Fatemi et al., 2013; Hong et al., 2011), without significant improvement in cognitive function or other symptoms and require replication of individual positive findings (Fatemi et al., 2013; Hong et al., 2011; Shim et al., 2012). A large multicenter trial of AZD3480, an α4β2 agonist, was negative for improvement in cognitive function (Velligan et al., 2012). Several small trials of nicotine have been mixed or negative (Table 3) (Barr et al., 2008; Depatie et al., 2002; Harris et al., 2004; Jubelt et al., 2008; Ramsay et al., 1970). A small trial of xanomeline, a type 1 and 4 muscarinic agonist, found that patients improved significantly on total BPRS and PANSS scores in addition to tests of verbal learning and short-term memory (Shekhar et al., 2008).

Trials of α7 nicotinic receptor agonists have been mixed. An initial multicenter trial of TC-5619 demonstrated significant improvement on cognitive tasks and negative symptoms (Lieberman et al., 2013), however, a larger multicenter trial was negative (Walling et al., 2016). A small trial of EVP-6124 demonstrated improvement in mismatch negativity and P300, but not other endophenotypic measures or cognitive testing (Preskorn et al., 2014). A larger multicenter trial of EVP-6124 demonstrated benefits on certain cognitive measures with differing performance on various cognitive tests between medication doses (Keefe et al., 2015). Unfortunately, EVP-6124 missed its primary endpoints in two subsequent Phase 3 trials (2016). A multicenter trial of RG-3487 was negative for improvement in MCCB scores, but in *post hoc* analyses found an improvement in negative symptoms in patients with moderate negative symptoms (Umbricht et al., 2014b). Two small trials of DMXB-A were mixed with one demonstrating improvement in SANS total score with no improvement in cognitive symptoms using the MCCB and another showing improvement in the RBANS total score, but only for the low dose arm of the trial (Freedman et al., 2008; Olincy et al., 2006). A recent multicenter trial of ABT-126 found no significant

Table 2
Clinical trials of experimental medications with serotonergic mechanisms.

Name (Mechanism)	Reference	Design	Sample	Length	Treatment Conditions	Primary Outcome	Results	Comment
Dimebon (5-HT6 antagonist and antihistamine)	(Morozova et al., 2012)	RCT, Add-on, Double Blind	56	2 months	Dimebon 20 mg/day, Placebo	PANSS, CGI, Calgary Depression Rating Scale, NSA-16, Cognitive battery	Improvement in NSA-16 scores, no differences otherwise	Add-on to risperidone, all male Russian patients
Ritanserin (5-HT2A/2C antagonist)	(Akhondzadeh et al., 2008b)	RCT, Add-on, Double Blind	40	8 weeks	Ritanserin 6 mg BID, Placebo	PANSS	Ritanserin was superior to placebo in decreasing negative symptoms and PANSS total scores at week 8	Add-on to risperidone, inpatients in Iran, acute phase of illness, required substantial negative symptoms on PANSS
Ritanserin (5-HT2A/2C antagonist)	(Abi-Saab et al., 2002)	Crossover, Monotherapy, Double Blind	22	4 individual visits	Ritanserin 10 mg vs placebo given 50 min prior to a 20 min infusion of mCPP (m-chlorophenylpiperazine (a propsychotic agent)) 0.1 mg/kg vs normal saline (placebo for mCPP)	BPRS, prolactin levels, cortisol levels	mCPP mildly elevated psychosis and behavioral activation as measured by BPRS and also raised serum prolactin and cortisol levels, ritanserin attenuated psychosis, behavioral activation and prolactin and cortisol levels, neither mCPP nor ritanserin had any effect on negative or mood symptoms	All male inpatients, following mCPP administration, fixed dose of both medications, pretreatment with ritanserin followed by mCPP
Ritanserin (5-HT2A/2C antagonist)	(Den Boer et al., 2000)	RCT, Add-on, Double Blind	160	8 weeks	Ritanserin 10 mg/day, Placebo	PANSS	No differences	Chronic and (sub)chronic patients
Vabicaserin (5-HT2C agonist)	(Shen et al., 2014)	RCT, Monotherapy, Double Blind	314	6 weeks	Vabicaserin 200 mg/day, Vabicaserin 400 mg/day, olanzapine 15 mg/day, Placebo	PANSS positive subscale	Improvement in PANSS positive subscale in Vabicaserin 200 mg/day and olanzapine 15 mg/day, no difference with Vabicaserin 400 mg/day	Active comparator trial, multicenter, acutely ill patients, required PANSS total greater than 70 and CGI ≥ 4
Pimavanserin (5-HT2A inverse agonist)	(Meltzer et al., 2012)	RCT, Add-on, Double Blind	423	6 weeks	Risperidone 2 mg/day + Placebo, Risperidone 2 mg/day + Pimavanserin 20 mg/day, Risperidone 6 mg/day + Placebo, Haloperidol 2 mg/day + Placebo, Haloperidol 2 mg/day + Pimavanserin 20 mg/day	PANSS total score	Pimavanserin + risperidone 2 mg had significantly more early responders than risperidone 2 mg and 6 mg + placebo groups, improvement with risperidone 2 mg + pimavanserin in PANSS total compared to risperidone 2 mg + placebo, no effect of augmenting haloperidol with pimavanserin	Add-on to risperidone and haloperidol, multicenter
Fananserin (5-HT2A and D4 antagonist)	(Truffinet et al., 1999)	RCT, Monotherapy, Double Blind	97	4 weeks	Fananserin 250 mg BID, Placebo	PANSS	No differences	Multicenter, inpatients
Mianserin (5-HT2A/2B/2C, α2 adrenergic, and H1 antagonist)	(Shiloh et al., 2002)	RCT, Add-on, Double Blind	18	6 weeks	Mianserin 30 mg/day, Placebo	BPRS, SAPS, SANS, HAMD	Improvement in BPRS scores, no differences otherwise	Add-on to haloperidol or perphenazine, treatment-resistant inpatients
Tropisetron (5-HT3 receptor antagonist)	(Noroozian et al., 2013)	RCT, Add-on, Double Blind	40	8 weeks	Tropisetron 5 mg BID, Placebo	PANSS	Tropisetron was superior to placebo in reducing PANSS total, negative, and general psychopathology scores, but no difference in positive subscale scores	Add-on to risperidone, chronic patients in Iran
Tropisetron (5-HT3 receptor antagonist)	(Zhang et al., 2012)	RCT, Add-on, Double Blind	40	10 days	Tropisetron 5 mg/day, 10 mg/day, 20 mg/day, Placebo	Auditory sensory gating P50 response, RBANS	Improvement in RBANS total score and P50 gating in all 3 dose groups, 10 mg improved immediate memory, 20 mg improved delayed memory	Add-on to risperidone
Tropisetron (5-HT3 receptor antagonist)	(Shiina et al., 2010)	RCT, Add-on, Double Blind	40	8 weeks	Tropisetron 10 mg/day, Placebo	Auditory sensory gating P50 response, CANTAB, PANSS, QLS	Improvement in P50 deficits (in non-smoking patients), visual attention, QLS, no differences otherwise	Add-on to risperidone, clinically stable Japanese outpatients

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Table 2 (*continued*)

Name (Mechanism)	Reference	Design	Sample	Length	Treatment Conditions	Primary Outcome	Results	Comment
Granisetron (5-HT3 receptor antagonist)	(Khodaie-Ardakani et al., 2013)	RCT, Add-on, Double Blind	40	8 weeks	Granisetron 1 mg BID, Placebo	PANSS negative subscale	Granisetron significantly reduced PANSS negative and total scores compared to placebo, no difference on positive or general psychopathology subscales	Add-on to risperidone, no significant placebo response in negative subscale
Ondansetron (5-HT3 receptor antagonist)	(Akhondzadeh et al., 2009)	RCT, Add-on, Double Blind	30	12 weeks	Ondansetron 8 mg/day, Placebo	PANSS, cognitive battery	Ondansetron significantly reduced PANSS negative subscale, general psychopathology, and total scores compared to placebo, ondansetron significantly improved visual memory based on visual reproduction, visual paired associate and figural memory sub tests of the revised Wechsler Memory Scale, no difference on positive subscale of PANSS	Add-on to risperidone, chronic and stable patients
Ondansetron (5-HT3 receptor antagonist)	(Zhang et al., 2006)	RCT, Add-on, Double Blind	121	12 weeks	Ondansetron 8 mg/day, Placebo	PANSS, CGI	Improvement in PANSS total, negative, general, cognitive subscales, no differences otherwise	Add-on to haloperidol, treatment resistant Chinese inpatients, multicenter trial
Ondansetron (5-HT3 receptor antagonist)	(Levkovitz et al., 2005)	Crossover, Add-on, Double Blind	21	1 week for each treatment arm, no wash out	Ondansetron 4 mg BID, Placebo	PANSS, CGI, Cognitive battery	Improvement in Rey-Osterrieth Complex Figure Test, no differences otherwise	Add-on to clozapine, stable outpatients
L-tryptophan (amino acid precursor to serotonin)	(Levkovitz et al., 2003)	Crossover, Add-on, Double Blind	21	4 days per treatment arm, no wash out	L-tryptophan 333 mg/day TID, Placebo	PANSS, CGI, Cognitive battery	Improvement on Paired Association, Rey-Osterrieth Complex Figure Test, Digit Symbol, Rivermead Behavioral Memory Tests, no differences otherwise	Add-on to haloperidol or perphenazine
L-Tryptophan (amino acid precursor to serotonin)	(Brewerton and Reus, 1983)	RCT, Add-on, Double Blind	16 (9 patients with Bipolar disorder, 7 patients with schizoaffective disorder)	3 weeks	L-tryptophan uptitrated to 3 g TID over 6 days, Placebo	Manic State Rating Scale and BPRS	L-tryptophan group had greater reduction in MSRS intensity and frequency score and total BPRS overall	Add-on to Lithium, included patients with Manic State Rating Scale score > 24 on admission, mixed prior exposure to lithium (some positive, non-responders, naïve), the Bipolar patients in the L-tryptophan group received greater quantities of neuroleptics than placebo (not the case for schizoaffective patients)
SR142801 (Neurokinin (NK3) antagonist), SR46349B (5-HT2A/2C antagonist), SR141716 (cannabinoid (CB1) antagonist), SR48692 (neurotensin (NTS1) antagonist)	(Meltzer et al., 2004)	RCT, Monotherapy, Double Blind	481	6 weeks	NK3 antagonist 200 mg/day, 5HT2A/2C antagonist 5 mg/day, CB1 antagonist 20 mg/day, NTS1 antagonist 180 mg/day, haloperidol 10 mg/day, Placebo	PANSS total, CGI, BPRS total score, BPRS psychosis cluster score	NK3 antagonist group improved CGI, BPRS psychosis score, 5HT2A/2C antagonist group improved PANSS and BPRS total scores, no differences otherwise	Comparator trial, multicenter, hospitalized at baseline through day 15, required PANSS > 65 and CGI > 4 at screening and baseline, efficacy analysis based on ITT

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Table 2 (*continued*)

Name (Mechanism)	Reference	Design	Sample	Length	Treatment Conditions	Primary Outcome	Results	Comment
MIN-101 (sigma 2 and 5HT2A antagonist)	(Davidson et al., 2017)	RCT, Monotherapy, Double Blind	244 total (234 in the ITT population)	12 weeks	MIN-101 32 mg/day or 64 mg/day or placebo	PANSS negative factor score, CGI, BNSS	MIN-101 groups improved on PANSS negative factor and negative symptoms, and the higher dose group improved on BNSS and CGI; no change on PANSS positive symptoms	Multicenter, all subjects off depot meds for a month, oral meds for at least 3 days, PANSS N1-N7 score ≥ 20; statistics of results were unclear

change in MCCB composite score overall, but showed a treatment-by-smoking status interaction with significant improvement in MCCB composite score and verbal learning, working memory, and attention domains of the MCCB in nonsmokers only (Table 3) (Haig et al., 2016).

5. Neuropeptides, including oxytocin and opioids

Oxytocin is a pituitary neuropeptide synthesized within the hypothalamus (Romano et al., 2015). It modulates a wide range of neurotransmitters, including dopamine. It has been suggested that its mechanism of action in schizophrenia may be via modulation of the mesolimbic dopaminergic system (Macdonald and Feifel, 2012). A number of trials have assessed oxytocin's effects as an add-on treatment in schizophrenia, especially effects on social cognition (Table 4). While some have demonstrated positive effects on only total PANSS scores, these trials, in particular more recent trials, have been largely negative, including trials examining effects on cognition or social cognition, though one trial found improvements on empathic accuracy (Davis et al., 2014) and another on smell identification (Lee et al., 2013).

Other neuropeptides such as desmopressin have putative mechanisms of action similar to oxytocin, while cholecystokinin and its analogue, ceruletide, are also thought to exert influence on the GABAergic system (Volk and Lewis, 2016). Dextromethorphan is a weak NMDA antagonist but may also act via anti-inflammatory and neurotrophic effects (Chen et al., 2012). Opioids, including endorphins and enkephalins, opioid antagonists, such as naltrexone, naloxone, and nalmefene, and buprenorphine, an opioid partial agonist, are thought to work via modulatory effects on neurotransmitters implicated in schizophrenia, such as dopamine (Nemeroff and Bissette, 1988). Although a few early trials were somewhat positive, these trials, including trials of opioid agonists (e.g., enkephalins, endorphins) and antagonists (e.g., naloxone), have also been mostly negative, although a small, crossover study of buprenorphine did demonstrate an acute effect for buprenorphine in unmedicated subjects (Table 4) (Schmauss et al., 1987). Other studies of neuropeptides either had very small samples sizes or involved very few doses and were mostly either negative or equivocal (Davis et al., 2013; Gibson et al., 2014; Peselow et al., 1987; Stein et al., 1984) (Berger et al., 1981; Gerner et al., 1980; Korsgaard et al., 1981; Verhoeven et al., 1981).

6. Hormones

Several hormones, particularly neurosteroids derived from cholesterol, have been tested for efficacy in schizophrenia (Table 5). Pregnenolone, for example, has purported stimulatory effects on both GABAergic and NMDAergic mechanisms (Marx et al., 2014). Estrogen, as well as raloxifene, an estrogen receptor modulator, also have wide ranging effects, including stimulating effects on neuroplasticity and neuroprotection (Weickert et al., 2015), as well as effects on neurotransmitter systems such as dopamine and serotonin (Fink et al., 1996). Prostaglandins may have stabilizing effects on neuronal membranes and may also modulate neurotransmitter systems, such as those related to dopamine and glutamate (Fenton et al., 2000). Numerous trials have been performed with these compounds, examining effects on positive, negative, and cognitive symptoms, as well as functioning. Overall, the data are mixed, with several trials demonstrating some benefit on at least one outcome (Marx et al., 2009; Ritsner et al., 2014; Usall et al., 2011). However, most trials and outcomes were negative. In addition, many of the trials did not perform intent-to-treat analyses, but rather reported completers analyses. For example, one trial examined erythropoietin, thought to have neuroprotective, anti-inflammatory, antioxidant, and other effects (Ehrenreich et al., 2004), in male subjects and reported cognitive but not symptomatic improvements (Ehrenreich et al., 2007). However, this trial essentially used a completers, rather than ITT analysis, and therefore should be interpreted with caution. There were also several trials in which multiple comparisons were not

Table 3
Clinical trials of experimental medications with cholinergic mechanisms.

Name (Mechanism)	Reference	Design	Sample	Length	Treatment Conditions	Primary Outcome	Results	Comment
Donepezil (acetylcholinesterase inhibitor)	(Keefe et al., 2008)	RCT, Add-on, Double Blind	250	12 weeks	Donepezil 10 mg/day, Placebo	CATIE cognitive battery	No differences	Multicenter, used LOCF
Donepezil (acetylcholinesterase inhibitor)	(Akhondzadeh et al., 2008a)	RCT, Add-on, Double Blind	30	12 weeks	Donepezil 5 mg/day x 4 weeks, then 10 mg/day, Placebo	PANSS, Cognitive Battery	Donepezil superior to placebo on PANSS negative subscale only at 12 weeks, no difference on any other measures	Add-on to risperidone, Chronically ill inpatients and outpatients in Iran
Donepezil (acetylcholinesterase inhibitor)	(Fagerlund et al., 2007)	RCT, Add-on, Double Blind	21 (11 completers)	4 months	Donepezil 5 mg/day, 10 mg/day, Placebo	PANSS, CANTAB	No differences	Add-on to ziprasidone
Donepezil (acetylcholinesterase inhibitor)	(Kohler et al., 2007)	RCT, Add-on, Double Blind	26	16 weeks	Donepezil 10 mg/day, Placebo	Cognitive battery	No differences	Outpatients, younger sample (ages 18 to 40)
Donepezil (acetylcholinesterase inhibitor)	(Lee, et al., 2007b)	RCT, Add-on, Double Blind	24	12 weeks	Donepezil 5 mg/day, Placebo	K-MMSE, BPRS, and cognitive battery	Improvement on K-MMSE, Rey Complex Figure Test immediate recall (week 8), no differences otherwise	Add-on to haloperidol, Korean inpatients
Donepezil (acetylcholinesterase inhibitor)	(Risch et al., 2007)	Crossover, Add-on, Double Blind	13	24 weeks	Donepezil 10 mg/day, Placebo	PANSS	Improvement in PANSS negative, total	Placebo patients worsened
Donepezil (acetylcholinesterase inhibitor)	(Mazeh et al., 2006)	Crossover, Add-on, Double Blind	20	24 weeks	Donepezil 10 mg/day, Placebo	PANSS, CGI, and ADAS-Cog	No differences	Elderly inpatients with cog impairment
Donepezil (acetylcholinesterase inhibitor)	(Freudenreich et al., 2005)	RCT, Add-on, Double Blind	36	8 weeks	Donepezil 10 mg/day, Placebo	PANSS, Cognitive battery	No differences	Chronically ill patients
Donepezil (acetylcholinesterase inhibitor)	(Erickson et al., 2005)	Crossover, Add-on, Double Blind	15	18 weeks total (including 2 weeks of washout)	Donepezil 5 mg/day, Placebo	PANSS, Cognitive battery	No differences	Inpatients in state hospitals
Donepezil (acetylcholinesterase inhibitor)	(Stryjer et al., 2004)	Crossover, Add-on, Double Blind	8	18 weeks (2 week wash out)	Donepezil 10 mg/day, Placebo	PANSS, CDS	No differences	Add-on to clozapine
Donepezil (acetylcholinesterase inhibitor)	(Tugal et al., 2004)	Crossover, Add-on, Double Blind	12	12 weeks (no wash out)	Donepezil 5 mg, Placebo	PANSS, Calgary Depression Scale, Cognitive battery	No differences	Stable outpatients, less cognitively impaired patients
Donepezil (acetylcholinesterase inhibitor)	(Friedman et al., 2002)	RCT, Add-on, Double Blind	36	12 weeks	Donepezil 10 mg/day, Placebo	PANSS, Cognitive battery	No differences	
Galantamine (AchEI, allosteric modulator of α7, α4β2 nicotinic receptors)	(Lindenmayer and Khan, 2011)	RCT, Add-on, Double Blind	32	6 months	Galantamine 12 mg BID, Placebo	PANSS, Cognitive battery	PANSS total worsened in galantamine group, social cognition, no differences otherwise	Part of a yearlong parent study of injectable risperidone
Galantamine (AchEI, allosteric modulator of α7, α4β2 nicotinic receptors)	(Conley et al., 2009)	RCT, Add-on, Double Blind	86	12 weeks	Galantamine 24 mg/day, Placebo	BPRS, CGI, SANS	Improvement in SANS alogia subfactor, no differences otherwise	Secondary analysis of 2008 Buchanan et al. study
Galantamine (AchEI, allosteric modulator of α7, α4β2 nicotinic receptors)	(Buchanan et al., 2008)	RCT, Add-on, Double Blind	86	12 weeks	Galantamine 24 mg/day, Placebo	Cognitive battery, SANS	Improvement in WAIS-III digit symbol test, SANS alogia subfactor, worsened performance on CPT, no differences otherwise	Required RBANS less than 90
Galantamine (AchEI, allosteric modulator of α7, α4β2 nicotinic receptors)	(Sacco et al., 2008)	RCT, Add-on, Double Blind	21	3 separate visits	Acute dose of Galantamine (0 mg, 4 mg, 8 mg followed by cognitive testing)	PANSS, Neurocognitive battery (CPT, Digit Span Forward, Stroop, TMT B)	No differences overall, non-smokers improved on CPT, Digit Span Forward, and Stroop, satiated smoker improved in visuospatial working memory, TMT B, and attentional consistency	Acute dosing, low dose of galantamine,
Galantamine (AchEI, allosteric modulator of α7, α4β2 nicotinic receptors)	(Dyer et al., 2008)	RCT, Add-on, Double Blind	20	8 weeks	Galantamine up to 32 mg/day, Placebo	Cognitive Battery, PANSS, SANS	Worsened performance on CPT, Stroop, Letter-Number span task, no differences otherwise	Nonsmoking patients, used LOCF

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Table 3 (*continued*)

Name (Mechanism)	Reference	Design	Sample	Length	Treatment Conditions	Primary Outcome	Results	Comment
Galantamine (AchEI, allosteric modulator of α7, α4β2 nicotinic receptors)	(Lee, et al., 2007b)	RCT, Add-on, Double Blind	24	12 weeks	Galantamine 8 mg/day for 6 weeks, then 16 mg/day for 6 weeks, Placebo	Cognitive battery	Improvement on recognition subfactor of Rey Complex Figure Test, no differences otherwise	Korean inpatients, required cognitive impairment
Galantamine (AchEI, allosteric modulator of α7, α4β2 nicotinic receptors)	(Schubert et al., 2006)	RCT, Add-on, Double Blind	16	8 weeks	Galantamine 24 mg BID, Placebo	RBANS total	Galantamine superior to on RBANS total	Add-on to risperidone, mild-moderate cognitive impairment
Rivastigmine (acetylcholinesterase inhibitor)	(Chouinard et al., 2007)	Crossover, Add-on, Double Blind	24	6 months	Rivastigmine 4.5 mg BID onwards, Placebo	Cambridge Neuropsychological Test Automated Battery (CANTAB) and PANSS	No differences	Inpatients, baseline cognitive deficit requirement using RBANS
Rivastigmine (acetylcholinesterase inhibitor)	(Sharma et al., 2006)	RCT, Add-on, Double Blind	21	24 weeks	Rivastigmine 6 mg BID, Placebo	PANSS, Cognitive Battery	No differences	Moderately cognitively impaired patients
Mecamylamine (non-competitive nicotinic receptor antagonist) and Varenicline (α7 nicotinic receptor agonist and α4β2 partial agonist)	(Roh et al., 2014)	Crossover, Add-On, Double Blind	30	Once weekly dosing for 3 study visits (1 dose of each medication in random order)	Mecamylamine 10 mg, Varenicline 1 mg, Placebo	Hit Reaction Time Variability (HRT-SD) on CPT-IP (assesses sustained attention)	Mecamylamine worsened performance on CPT-IP HRT-SD compared to varenicline in SCZ patients and healthy volunteers, however, neither mecamylamine nor varenicline differed from placebo, volunteers, no difference between varenicline and placebo	Single dose, crossover study, patients were stable, outpatient, nonsmoking
Varenicline (α7 nicotinic receptor agonist and α4β2 partial agonist)	(Fatemi et al., 2013)	RCT, Add-On, Double Blind	24 (17 completers)	12 weeks	Varenicline 1 mg BID, Bupropion SR 150 mg BID, Placebo	Abstinence via self-report, exhaled carbon monoxide, serum/urine levels of nicotine and cotinine, BPRS, SAPS/SANS	Reduction in urge to smoke for varenicline and bupropion, no differences for varenicline otherwise	Smoking cessation study with active comparator, medication well tolerated
Varenicline (α7 nicotinic receptor agonist and α4β2 partial agonist)	(Hong et al., 2011)	RCT, Add-on, Double Blind	69	8 weeks	Varenicline 1 mg/day (week 1, 0.5 mg/day, weeks 2–8, 0.5 mg BID), placebo	Prepulse Inhibition, Startle Reactivity, P50 gating, Smooth Pursuit Eye Movement, Antisaccade and Memory Saccade, Cognitive Battery Cigarettes smoked per day	Improvement in startle reactivity, reduced P50 S2/S1 ratio in nonsmoking subjects, antisaccadic error rate, cigarettes per day, no differences otherwise	Outpatients, divided in smoking and nonsmoking subjects
Varenicline (α7 nicotinic receptor agonist and α4β2 partial agonist)	(Shim et al., 2012)	RCT, Add-on, Double Blind	120	8 weeks	Varenicline 0.5 mg for days 1–3, 0.5 mg BID for days 4–7, then 1 mg BID for weeks 2–8, Placebo	Cognitive battery, PANSS	Improvement on Digit Symbol Substitution Test, Wisconsin Card Sorting Test in smokers, no differences otherwise	Stable Korean outpatients, multicenter trial
Xanomeline (type 1 and 4 muscarinic agonist, type 5 muscarinic antagonist)	(Shekhar et al., 2008)	RCT, Add-on, Double Blind	20	4 weeks	Xanomeline 75 mg TID, Placebo	PANSS, BPRS, CGI total scores	Improvement in BPRS, PANSS total, positive, and negative subscales, no differences otherwise	Acutely ill or treatment-refractory inpatients
Trihexyphenidyl (type 1 muscarinic antagonist)	(Goff et al., 1994)	Crossover, Monotherapy, Double Blind	17	4 weeks	Trihexyphenidyl 5 mg BID, Placebo	BPRS, HAM-D, SANS	No differences	Outpatients off of medications for at least 2 months
Nicotine	(Barr et al., 2008)	Crossover, Add-on, Double Blind	28 patients with schizophrenia, 32 healthy controls	3 visits: Baseline testing, drug, and placebo with testing 3 h later	Nicotine 14 mg transdermal patch, Placebo	CPT identical pairs hit reaction time	Greater improvement in several CPT-IP endpoints in patients vs. healthy controls	Used non-psychiatric controls, all patients were nonsmoking
Nicotine	(Jubelt et al., 2008)	Crossover, Add-on, Double Blind	10 patients with schizophrenia, 12 healthy controls	Two study visits (roughly 1–2 weeks between visits)	Single dose nicotine transdermal 14 mg, Placebo	CPT, Stroop Test, Letter Number Sequencing, Grooved Pegboard	Reduction of false alarms in both populations (no between group differences), no differences otherwise	Non-smoking patients with schizophrenia and healthy controls

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Table 3 (*continued*)

Name (Mechanism)	Reference	Design	Sample	Length	Treatment Conditions	Primary Outcome	Results	Comment
Nicotine	(Harris et al., 2004)	Crossover, Add-on, Double Blind	20	Two study visits, 1 week apart	Nicotine gum 6 mg, Placebo	RBANS	No differences	Smoking and nonsmoking patients
Nicotine	(Depatie et al., 2002)	Crossover, Add-on, Double Blind	15 patients with schizophrenia and 14 healthy controls	2 Visits: Testing 8 h after the patch applied, at least one week washout	Nicotine 14 mg or placebo transdermal patch applied 9.5 h after abstaining from smoking.	CPT-Identical pairs, antisaccade and visually guided saccade control task, smooth pursuit task	Improvement in CPT performance in patients only, antisaccade errors in both groups, no differences otherwise	Used healthy controls, smoking patients only
Nicotinic Acid	(Ramsay et al., 1970)	RCT, Add-on, Double Blind	30	6 months	Nicotinic acid 1500 mg/day BID, Placebo	BPRS, MMPI, Hoffer-Osmond Diagnostic Test	No differences	Newly admitted inpatients
ABT-126 (α7 nicotinic receptor partial agonist)	(Haig et al., 2016)	RCT, Add-on, Double Blind	207	12 weeks	ABT-126 10 mg/day, 25 mg/day, Placebo	Change in baseline to final MCCB composite, MCCB domain scores, UPSA, PANSS, CGI-S, CANTAB, NSA	Treatment-by-smoking status interaction with improvement in baseline to final MCCB for nonsmoking subjects, no differences otherwise	Multicenter trial, included both smoking and nonsmoking patients
EVP-6124 (α7 nicotinic receptor partial agonist)	(Preskorn et al., 2014)	RCT, Add-on, Double Blind	21	3 weeks	EVP-6124 0.3 mg/day, 1 mg/day, Placebo	EEG P50, N100, P300, Mismatch Negativity, CogState Battery	Dose dependent Improvement in MMN and P300, no differences otherwise	Stable inpatients
EVP-6124 (α7 nicotinic receptor partial agonist)	(Keefe et al., 2015)	RCT, Add-on, Double Blind	319	12 weeks	EVP-6124 0.27 mg/day, 0.9 mg/day, Placebo	Overall Cognition Index (OCI), MCCB, Schizophrenia Cognition Rating Scale (SCoRS) total score and global rating, PANSS	Improvement OCI score for 0.27 mg dose, SCoRS total for 0.9 mg, PANSS cognitive and negative scales for 0.9 mg	Multinational study, stable patients not on clozapine, used LOCF
RG-3487 (α7 nicotinic receptor partial agonist)	(Umbricht et al., 2014b)	RCT, Add-on, Double Blind	215	8 weeks	RG-3487 5 mg/day, 15 mg/day, 50 mg/day, Placebo	Change in MCCB	Improvement NSA total/global scores in 5 mg, 50 mg dose groups, no differences otherwise	Baseline PANSS total score less than 70, stable patients
TC-5619 (α7 nicotinic receptor partial agonist)	(Walling et al., 2016)	RCT, Add-on, Double Blind	477	24 weeks	TC-5619 5 mg/day, 50 mg/day, Placebo	SANS, Cogstate Schizophrenia Battery (CSB), UPSA-B	No differences	Multicenter trial
TC-5619 (α7 nicotinic receptor partial agonist)	(Lieberman et al., 2013)	RCT, Add-on, Double Blind	185	12 weeks	TC-5619 1 mg/day for weeks 1–4, then 5 mg/day for weeks 4–8, then 25 mg/day for weeks 8–12	Groton Maze Learning Task, SANS	Improvement on Groton Maze task at week 4 only, SANS at week 12 only, no differences otherwise	Multinational trial
DMXB-A (α7 nicotinic receptor partial agonist)	(Freedman et al., 2008)	Crossover, Add-on, Double Blind	31	9 weeks total (1 week washout)	DMXB-A 75 mg BID, 150 mg BID, Placebo	Change in MCCB, SANS, BPRS	Improvement in SANS total in DMXB-A 150 mg BID group, no differences otherwise	Stable patients, test repetition effects noted
DMXB-A (α7 nicotinic receptor partial agonist)	(Olincy et al., 2006)	Crossover, Add-on, Double Blind	12	3 single day trials	First dose of DMXB-A 150 mg or 75 mg followed 2 h later by supplemental half dose (75 mg or 37.5 mg)	P50 auditory evoked potential suppression, RBANS total	Improvement in RBANS total and reduced P50 amplitude in DMXB-A 75mg/37.5 mg dose only, no differences otherwise	Visit effect detected
AZD3480 (α4β2 agonist)	(Velligan et al., 2012)	RCT, Add-on, Double Blind	440	12 weeks	AZD3480 5 mg/day, 20 mg/day, 35 mg/day, 100 mg/day (depending on 2D6 status), Placebo	Change in cognition via IntegNeuro cognitive battery	No differences	Moderately ill patients, included smokers

Table 4
Clinical trials of experimental medications with neuropeptidergic/opioid mechanisms.

Name (Mechanism)	Reference	Design	Sample	Length	Treatment Condition	Primary Outcome	Results	Comment
Oxytocin	(Dagani et al., 2016)	Crossover, Add on, Double Blind	32	8 Months (4 month each)	Placebo, 40 IU IN Oxytocin QD	PANSS Total	No Difference	Early Stage Patients
Oxytocin	(Cacciotti-Saija et al., 2015)	RCT, Add on, Double Blind	52	6 weeks	Placebo, 12 IU Bid Oxytocin	SAPS, SANS, RMET and SFS (social cognition and functioning)	No differences	Added to group social cognition training; Early Stage Patients
Oxytocin	(Davis et al., 2014)	RCT, Add on, Double Blind	27	Twice a week for 6 weeks	Placebo, 50IU IN Oxytocin QD Twice a week	Social Cognition, MATRICS, BPRS, CAINS	No differences, except better on empathic accuracy	Add on to social cognition skills training
Oxytocin	(Lee et al., 2013)	RCT, Add on, Double Blind	28	3 weeks	20 IU IN Oxytocin BID, Placebo	UPSIT (smell identification), BPRS, SANS, CGI	Smell identification improved, placebo was superior on total BPRS	
Oxytocin	(Modabbernia et al., 2013)	RCT, Add on, Double Blind	40	8 weeks	40 IU IN BID, Placebo	PANSS	Improvement on all PANSS scales	Add on to risperidone, inpatient
Oxytocin	(Pedersen et al., 2011)	RCT, Add on, Double Blind	20	2 weeks	24 IU BID, Placebo	Social cognition and PANSS	Improvement on PANSS total only, no other variables	
Oxytocin	(Feifel et al., 2010)	Crossover, Add on, Double Blind	15	3 weeks	40 IU IN BID, Placebo	PANSS, CGI	Improvement on PANSS total only	
Desmopressin	(Hosseini et al., 2014)	RCT, Add on, Double Blind	40 (should be 44)	8 weeks	20 mcg IN, Placebo	PANSS, HDRS	Improvement on PANSS Total, Negative, and General	Add on risperidone, completers and LOCF rather than ITT analysis
AZD2624 (neurokinin-3 antagonist)	(Litman et al., 2014)	RCT, Monotherapy, Double Blind		4 weeks	40 mg AZD2624, placebo, 15 mg olanzapine	PANSS, CGI, CogState	No benefit, some worsening	Inpatient, used ITT but LOCF
CCK-8 (cholecystokinin agonist)	(Nair et al., 1984)	RCT, Add on, Double Blind	18	8 weeks	Weekly injections of 10 μg CCK-8 or placebo	BPRS	Improvement	Treatment Resistant
Ceruletide (cholecystokinin analogue)	(Mizuki et al., 1988)	Crossover, Add on, Double Blind	8	3 weeks	0.8 μg/kg ceruletide IM weekly for 3 weeks or placebo	BPRS	No Differences	
Ceruletide (cholecystokinin analogue)	(Albus et al., 1986)	RCT, Add on, Double Blind	20	3 weeks	0.8 μg/kg ceruletide IM weekly for 3 weeks or placebo	BPRS	No Differences	
Ceruletide (cholecystokinin analogue) and Desenkephalin gamma endorphin	(Verhoeven et al., 1986)	RCT, Add on, Double Blind	44	3 weeks (7 doses)	3 mg DGE or 40 μg ceruletide IM or placebo, each over 3 weeks	BPRS	Improvements for both treatment groups	
Ceruletide (cholecystokinin analogue)	(Mattes et al., 1985)	RCT, Add on, Double Blind	27	10 days	17 does of 0.6 μg/kg or placebo	BPRS, SCL-90	No differences	
Ceruletide (cholecystokinin analogue)	(Hommer et al., 1984)	Crossover, Add on, Double Blind	8	4 days each	0.3–0.6 μg/kg IM daily for 4 days, or placebo	BPRS	No differences	
Dextromethorphan (NMDA antagonist, anti-inflammatory, neurotrophic)	(Chen et al., 2012)	RCT, Add on, Double Blind	137	11 weeks	60 mg/day dextromethorphan or placebo	PANSS	No differences	All on risperidone; no between group analyses, used an OC analysis
Naltrexone (opioid receptor antagonist)	(Sernyak et al., 1998)	RCT, Add on, Double Blind	21	3 weeks	200 mg naltrexone qd, placebo	BPRS	No differences	
Naltrexone (opioid receptor antagonist)	(Gitlin et al., 1981)	Crossover, Add on and Monotherapy, Double Blind	7	14 days	200 mg naltrexone PO for 7d then placebo	BPRS	No differences	
Naloxone (opioid receptor antagonist)	(Verhoeven et al., 1984a)	Cross over, Add on, Double Blind	10	4 days	20 mg naloxone SC or placebo, 4 days each	BPRS	No differences	Add on
Naloxone (opioid receptor antagonist)	(Pickar et al., 1989)	Crossover, Add on, Double Blind	43	4 days	0.3 mg/kg naloxone IV qd for 4d then placebo	BPRS	No differences	multisite
FK 33–824 (methionine encephalin; opioid agonist)	(Joergensen and Fog, 1986)	Crossover, Add on, Double Blind	10	3 weeks	1 week FK33-824 2 mg IM daily, one week placebo, one week pentobarbital control 25 mg IM qd	BPRS	No difference	

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Table 4 (*continued*)

Name (Mechanism)	Reference	Design	Sample	Length	Treatment Condition	Primary Outcome	Results	Comment
Des-tyr1-gamma endorphin (opioid agonist)	(Verhoeven et al., 1984b)	Crossover, Monotherapy, Double Blind	18	20 days total	1 mg IM DTG endorphin daily or placebo each for 10 days	BPRS	Improvement for BPRS group	
Des-tyr1-gamma endorphin (opioid agonist)	(Volavka et al., 1983)	Cross over, Add on, Double Blind	9	16 days total	1 mg IM DTG endorphin daily for 8 days and placebo daily	BPRS	Improvement only on day 3	
Des-tyr1-gamma endorphin (opioid agonist)	(Verhoeven et al., 1982)	RCT, Add on, Double Blind	19 (13 active, 6 placebo)	10 days	3 mg IM DTG endorphin daily for 10 days or placebo	BPRS	Improvement on BPRS	
Des enkephalin gamma endorphin (opioid agonist)	(Montgomery et al., 1992)	RCT, Monotherapy, Double Blind	94	4 weeks	10 mg IM qd or thioridazine 400 mg or placebo	Montgomery Schizophrenia Scale (MSS) and BPRS	Thioridazine did better	
Buprenorphine (partial opioid agonist)	(Schmauss et al., 1987)	Crossover, Montherapy, Double Blind	10	4 days total	0.2 mg bup SL or placebo	Inpatient Multidimensional Inpatient Rating Scale	Acute Benefit for Buprenorphine	
Nalmefene (opioid antagonist)	(Rapaport et al., 1993)	RCT, Add on, Double Blind	10	~30 days	40–50 mg per day	BPRS and SANS	Mostly negative, just decrease BPRS thinking disturbance	

performed when they would have otherwise been necessary (Table 5). Finally, other trials involving very few doses or subjects were generally negative and not included (Bigelow et al., 1975; Clark et al., 1975).

7. Dopaminergic medications

As stated above, all currently available antipsychotic medications work by antagonizing the D2/D3 receptor system. One newer medication that has demonstrated efficacy, though not in all studies, in schizophrenia is cariprazine (Durgam et al., 2014, 2016; Kane et al., 2015), a partial agonist which is also D3 preferring (Girgis et al., 2016a), though is otherwise similar to currently available medications (Supplementary Table 1). Cariprazine is now FDA approved. ABT-925, a D3 antagonist, however, did not show benefit (Redden et al., 2011), while pramipexole, a D3 agonist, did (Kelleher et al., 2012). D4 receptor antagonists, part of the D2/D3 family of dopamine receptors, have also failed to demonstrate efficacy (Corrigan et al., 2004; Kramer et al., 1997). Other dopaminergic mechanisms generally aim to increase dopaminergic transmission at cortical dopamine receptors, with the goals of targeting negative and cognitive symptoms. These mechanisms of action include inhibiting enzymes involved in synaptic degradation of dopamine (e.g., entacapone) (Kaphzan et al., 2014), or enhancing dopamine release (e.g., amantadine) (Silver et al., 2005). These trials have largely been negative (Supplementary Table 1). One particular trial, the first testing a full D1 receptor agonist, particularly tested the low dose theory of D1 stimulation and found that while this strategy may be effective in non-human primates (Castner et al., 2000), it does not translate to humans and future trials of D1 agonists should use agents that reach greater and measurable levels of occupancy (Girgis et al., 2016b). Apomorphine, L-DOPA, and tyrosine (a precursor of dopamine) have also been tried with mixed results, generally in single dose or smaller trials (Buchanan et al., 1975; Deutsch et al., 1994; Ferrier et al., 1984; Levy et al., 1984).

8. Metabolic medications

Thiazolidinediones such as pioglitazone and rosiglitazone are thought to exert anti-inflammatory effects via their PPAR-gamma agonism (Supplementary Table 2) (Iranpour et al., 2016). Trials of these agents have been largely negative, while others have not clearly used ITT analyses. HMG-CoA reductase inhibitors, ("statins" such as pravastatin) have also been investigated in schizophrenia with primarily negative results. These medications are also thought to exert anti-inflammatory effects (Vincenzi et al., 2014). Insulin has also not demonstrated benefit in schizophrenia (Fan et al., 2013).

9. Vitamins/naturopathic medications

A number of vitamins and naturally occurring substances have been tested in schizophrenia, primarily as supplementation, though many have other potentially beneficial properties. Resveratrol is naturally found in a variety of plants and is thought to have anti-inflammatory properties (Supplementary Table 3) (Zortea et al., 2016). A number of other compounds such as ginkgo biloba (Maitra et al., 1995), L-carnosine (Chengappa et al., 2012), s-adenosyl methionine (Strous et al., 2009), omega 3 fatty acids (Amminger et al., 2010), and L-lysine, which is thought to limit nitric oxide synthesis (Zeinoddini et al., 2014), have a variety of effects, including anti-inflammatory and anti-oxidant, as well as potential effects on a number of neurotransmitter systems involved in schizophrenia. N-acetylcysteine, a precursor of glutathione, may work by normalizing glutathione levels and glutamatergic function via effects on the cystine-glutamate antiporter (Baker et al., 2008). The potential of other vitamins, such as folate, in schizophrenia is thought to be related to the need to replace deficiencies observed in schizophrenia. Among this group, the majority of trials and outcomes were negative. One trial found a benefit for supplementation with folate/B12

Table 5
Clinical trials of experimental medications with hormone-based mechanisms.

Name (Mechanism)	Reference	Design	Sample	Length	Treatment Conditions	Primary Outcome	Results	Comment
Pregnenolone (neurosteroid)	(Marx et al., 2014)	RCT, Add on, Double Blind	120	8 weeks	500 mg pregnenolone or placebo	MATRCIS, BACS, SANS, PANSS, UPSA	No differences except improvement on UPSA	
Pregnenolone (neurosteroid)	(Ritsner et al., 2014)	RCT, Add on, Double Blind	60	8 weeks	50 mg pregnenolone or placebo	PANSS, SANS, GAF	Better on SANS and PANSS neg only	Early Stage
Pregnenolone and DHEA (neurosteroid)	(Ritsner et al., 2010)	RCT, Add on, Double Blind	44	8 weeks	30 mg preg, 200 mg preg, 400 mg DHEA, placebo	PANSS, CGI, CANTAB	Only 30 mg group did better on PANSS positive	Completers analysis with 4 groups and 44 total subjects
Pregnenolone (neurosteroid)	(Marx et al., 2009)	RCT, Add on, Double Blind	18	8 weeks	200 mg pregnenolone	SANS, PANSS, BACS, MATRICS, CDRS	Improvement on SANS	
Raloxifene (estrogen receptor modulator)	(Khodaie-Ardakani et al., 2015)	RCT, Add on, Double Blind	42	8 weeks	Risp 6 mg/day and 120 mg raloxifene or placebo	PANSS, HDRS	Improvement on PANSS total and neg and gen psychopathology	Add on to risperidone as all were off meds at start
Raloxifene (estrogen receptor modulator)	(Weickert et al., 2015)	Crossover for half of study, RCT, Add on, Double Blind	71 (79 for first 6 weeks)	13 weeks total	120 mg/day raloxifene or placebo	WAIS III, PANSS	Improvement on TMT-A at 13 weeks, no symptomatic differences	Not an ITT analysis
Raloxifene (estrogen receptor modulator)	(Huerta-Ramos et al., 2014)	RCT, Add on, Double Blind	33 (less for most tests)	12 weeks	60 mg/day raloxifene	Several cognitive measures, PANSS	Minor cognitive improvements, no symptomatic differences	Postmenopausal women only; no correction for multiple comparisons
Raloxifene (estrogen receptor modulator)	(Usall et al., 2011)	RCT, Add on, Double Blind	32	12 weeks	60 mg/day raloxifene	PANSS	Improvement on all PANSS scores	Postmenopausal women only; no correction for multiple comparisons
Raloxifene (estrogen receptor modulator)	(Kulkarni et al., 2016)	RCT, Add on, Double Blind	56	12 weeks	120 mg/day raloxifene or placebo	PANSS, RBANS, MADRES	Improvement on total PANSS and General PANSS	Peri- and postmenopausal women only; unclear how missing data were handled
Raloxifene (estrogen receptor modulator)	(Usall et al., 2016)	RCT, Add on, Double Blind	70	24 weeks	60 mg/day raloxifene or placebo	PANSS, SANS	Improvement on PANSS total, negative, and general, and SANS alogia scales	Postmenopausal women only; used LOCF
Estrogen (neurosteroid)	(Bergemann et al., 2005)	Crossover, Add on, Double Blind	39	8 months (crossover ABAB	2 mg/day 17beta estradiol	PANSS, BDI	No differences	Completers analysis, hypoestrogenic women only
Estrogen (neurosteroid)	(Louza et al., 2004)	RCT, Add on, Double Blind	42	4 weeks	0.625 mg conj. Estrogen and 5 mg Haldol or just Haldol and placebo	BPRS	No differences	Completers analysis; women only
Estrogen (neurosteroid)	(Akhondzadeh et al., 2003)	RCT, Add on, Double Blind	32	8 weeks	0.5 mgm ethinyl estradiol and 5 mg Haldol or Haldol and placebo	PANSS	Improvement in PANSS total, positive and general	Subjects were placed on both meds at start
Estrogen (neurosteroid)	(Kulkarni et al., 2002)	RCT, Add on, Double Blind	36	4 weeks	50μg, 100 μg estradiol or placebo	PANSS	Improvement in high dose group on PANSS total, positive, and general	
Erythropoietin	(Ehrenreich et al., 2007)	RCT, Add on, Double Blind	39	12 weeks	40 000 IU of EPO-beta weekly or placebo infusion	RBANS, PANSS	Improvement in RBANS, not PANSS	completers analysis, only males
DHEA (neurosteroid)	(Strous et al., 2007)	RCT, Add on, Double Blind	40	12 weeks	150 mg/day DHEA or placebo	SANS, PANSS, CDSS, cognitive measures	Improvement on SANS, not PANSS (or subscales) or CDSS or cognitive scales	Add on to olanzapine
DHEA (neurosteroid)	(Ritsner et al., 2006)	RCT, Add on, Double Blind	55	12 weeks	100 mg bid DHEA or placebo (each for 6 weeks)	PANSS, CANTAB	No differences on PANSS, some improvement on visual sustained attention and visual and movement skills	Completers analysis
DHEA (neurosteroid)	(Strous et al., 2003)	RCT, Add on, Double Blind			100 mg qd DHEA	PANSS, SANS, HAM D and HAM A	No on PANSS total, neg, and positive, yes on PANSS general and SANS and HAM D and HAM A	Modified completers analysis and LOCF
Testosterone (neurosteroid)	(Ko et al., 2008)	RCT, Add on, Double Blind	30	4 weeks	1% testosterone gel (5 gm) daily	PANSS	Improvement on PANSS negative only	younger male smokers, LOCF
			19	2 weeks			No differences	completers analysis

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Table 5 (*continued*)

Name (Mechanism)	Reference	Design	Sample	Length	Treatment Conditions	Primary Outcome	Results	Comment
Mifepristone (anti-neurosteroid and anti-glucocorticoid)	(Gallagher et al., 2005)	Crossover, Add on, Double Blind			600 mg mifepristone or placebo one week each	CANTAB and Wechsler items; BPRS, CDRS, HDRS		
Thyrotropin releasing hormone	(Lindstrom et al., 1977)	Cross over, Monotherapy, Double Blind	10	4 days	600μg TRH for 4 days and placebo 4 days, IV	CPRS (Comprehensive Psychopathological Rating Scale; NOSIE	No difference	
Dihomo gammalinolenic acid (Prostaglandin E1 precursor)	(Vaddadi et al., 1986)	RCT, Add on, Double Blind	21	4 months	Three groups: 1) up to 1 gm/day DHLA and AP; 2) up to 1 gm./day DHLA and placebo AP; 3) placebo DHLA and placebo AP	BPRS	No differences	All treatment refractory and began study on stable depot meds

on the SANS and only when genetic variation for folate absorption was taken into account (Roffman et al., 2013). Another trial reported that supplementation with omega 3 fatty acids decreased risk of conversion to psychosis in a sample at high risk for psychosis (Amminger et al., 2010). Otherwise, trials were generally negative or mixed (Supplementary Table 3). There were also several trials with preliminarily positive data that used last observation carried forward for missing data, or variations of a completers analysis, rather than intent to treat. Other trials of L-lysine (Wass et al., 2011), ginseng (Chen and Hui, 2012), and megavitamins were either negative, single blind, or did not examine between group differences.

10. Histaminergic medications

Histaminergic medications that have been examined in schizophrenia are mostly antagonists at the H3 receptor, which releases neurotransmitters such as dopamine, acetylcholine, and norepinephrine (Brown et al., 2001). Trials of H3 antagonists have been negative (Supplementary Table 4). Histamine-2 receptor activity is also linked with the activity of several neurotransmitters relevant to schizophrenia, such as dopamine and GABA, and one study using famotidine was positive though an LOCF analysis was used (Meskanen et al., 2013). Cyproheptadine, which acts as an antagonist or inverse agonist at numerous receptor subtypes, including histamine receptors, has also been tried with equivocal results (Akhondzadeh et al., 1999).

11. Inflammation/infection

Antibiotics and anti-inflammatory agents have been tested in individuals with schizophrenia. Several antibiotic agents have putative mechanisms of action directly related to their antibiotic effects, such as artemether, azithromycin, trimethoprim, and artemisinin for toxoplasma gondii (Dickerson et al., 2009b, 2011; Shibre et al., 2010; Wang et al., 2014), and valacyclovir for herpes (Prasad et al., 2013) or cytomegalovirus (Supplementary Table 5) (Dickerson et al., 2009a). These trials generally recruited individuals who were seropositive for the microbe in question, and were mostly negative. Anti-inflammatory agents such as celecoxib, hydroxychloroquine, and aspirin have been used as non-specific anti-inflammatory agents to counter the cytokine elevations and other inflammatory abnormalities in schizophrenia (Brown and Derkits, 2010; Girgis et al., 2014). Trials of celecoxib were mixed, with two positive and two negative. However, three of the trials utilized last observation carried forward and are harder to interpret (Supplementary Table 5). In addition, one trial of 1000 mg per day of aspirin as add on treatment demonstrated improvements in PANSS total and positive symptoms (Laan et al., 2010).

12. Miscellaneous

A number of other mechanisms have been targeted with limited success (Supplementary Table 6). Davunetide is a microtubule stabilizing agent that did not show efficacy (Javitt et al., 2012). Adenosine uptake inhibitors such as dipyridamole and propentofylline, which also putatively decrease dopamine release, were found to have positive effects on PANSS total, general, and positive symptom scores in one study (Akhondzadeh et al., 2000) but not in others (Salimi et al., 2008; Wonodi et al., 2011). Trials with allopurinol, which also putatively increases adenosine levels by inhibiting xanthine oxidase, are also mixed (Weiser et al., 2012a). Trials of rimonabant, an inverse agonist of the cannabinoid 1 receptor (Kelly et al., 2011), and cannabidiol, which increases levels of anandamide (Leweke et al., 2012), were mostly negative. Trials of sildenafil, a phosphodiesterase 5 inhibitor, which is thought to work downstream from the NMDA receptor, were mixed (Supplementary Table 6) (Akhondzadeh et al., 2011; Goff et al., 2009). One small crossover trial of oxygen supplementation demonstrated some symptomatic and cognitive improvements (Bloch et al., 2012).

Prazosin, an alpha 1 adrenergic receptor antagonist, was not effective in schizophrenia, as was MK-077, a partial agonist at the GABA A alpha2/alpha3 receptor (Buchanan et al., 2011; Lewis et al., 2008). Finally, while nilvadipine, a non-specific calcium channel antagonist, demonstrated some efficacy as an add on agent (Yamada et al., 1996), flunarizine, which also possesses some D2 antagonist activity, did not differentiate from haloperidol (Bisol et al., 2008), and a trial of MK-8998, a specific t-type calcium channel antagonist, was negative (Supplementary Table 7) (Egan et al., 2013).

13. Discussion and recommedations

In this paper, we comprehensively reviewed experimental, non-D2 antagonist clinical trials in schizophrenia. The dozens of different mechanisms of action investigated reflect not only the complexity of the underlying pathophysiology of the illness, but the important search for effective treatments of cognitive and negative symptoms. There appears to be a signal suggesting that enhancement of glutamatergic neurotransmission with glycine and sarcosine, but not D-cycloserine or D-serine, is associated with a modest improvement of negative symptoms, but only when added to non-clozapine antipsychotics. Interestingly, a recent trial of sodium benzoate adjuvant therapy improved symptomatology of patients with clozapine-resistant schizophrenia (Lin et al., 2017a) and memantine, an NMDA receptor antagonist, appears to be more effective when added to clozapine than other antipsychotics though these results require replication. These results are corroborated by a meta-analysis of NMDA receptor modulators by Singh et al., who demonstrated an overall effect size of −0.27 for negative symptoms, with slightly larger effect size for the aforementioned medications when added to non-clozapine anti-psychotics (Singh and Singh, 2011). These results also provide additional evidence to the existing literature demonstrating clozapine's ability to potentiate NMDA receptor-mediated neurotransmission, which may be a clue to its superior efficacy (Evins et al., 1997; Javitt et al., 2005; Malhotra et al., 1997; Melone et al., 2001; Yamamori et al., 2014).

Modulation of the neuronal nicotinic acetylcholine receptor appears to be the most promising current target for the improvement of cognitive symptoms. Though non-specific increases of cholinergic neurotransmission with acetylcholinesterase inhibitors do not appear to be effective, targeted agonists of the α7 nicotinic receptor have demonstrated some positive results for cognitive function in well-designed trials. However, these benefits appear in subdomain, rather than composite, measures of cognitive function, and may be more likely to be detected in subpopulations of the patient population such as non-smokers (Haig et al., 2016).

Unfortunately, despite a handful of potentially promising targets, due to significant methodologic limitations and lack of replication, we are unable to confidently state that any of the experimental treatments covered in this review are effective for the treatment of schizophrenia. This conclusion is further corroborated by a recent analysis of meta-analyses of 42 cotreatment strategies in schizophrenia in which the authors were unable to recommend any adjunctive pharmacotherapy (Correll et al., 2017). While their analysis focused mostly on medications we did not review (e.g. antidepressants, mood stabilizers), there was some overlap (e.g. NSAIDs, hormonal treatments). In this discussion, we will review the methodologic and theoretical reasons for why this is and suggest possible ways to limit or reduce these shortcomings in the future.

14. Methodologic issues

There are a number of methodological issues in the studies we reviewed that could contribute to both type I (false positive) and type II errors (false negative). First, the majority of studies reviewed were significantly underpowered to detect a clinically meaningful effect. Just 16% of the 250 trials reviewed had sample sizes over 100 subjects and only another 16% had over 50 subjects. Given the exploratory nature of experimental studies and the resources associated with larger, multicenter clinical trials, it is understandable that the majority of these trials were small. However, the results, especially when not replicated, should be interpreted with caution. Additionally, many of the trials, particularly those prior to the past decade, failed to clearly define their primary and secondary outcomes *a priori* and did not account for multiple comparisons when reporting their significant results. Along these lines, missing data were often handled by performing last observation carried forward or modifications of “completers” analyses, which violate the necessary assumptions of an intent to treat analysis and are not considered valid methods for clinical trials in medicine (Lachin, 2000).

Rising placebo effect rates may also contribute to type II error. In a meta-analysis of anti-psychotic trials since the 1960s, Rutherford et al. highlighted a significant rise in the rate of the placebo effect. The average placebo-treated patient in the 1960s demonstrated a worsening of 3.5 BPRS points as opposed to an improvement of 3.2 BPRS points for a placebo-treated patient in the 2000s. Furthermore, the magnitude of the placebo effect increases with increasing sample size (and subsequently number of study sites), which creates a challenge for balancing statistical power with a rising placebo effect (Rutherford et al., 2014).

The variability of trial designs reviewed is another contributing factor to replication failure and potential type I or type II error. Differences in trial design (parallel-group vs. crossover), trial duration, trial size, number of sites, severity of schizophrenia, phase of illness, medication dosage, primary and secondary outcomes, and selection of assessment tools make comparing studies even more difficult. Each of these factors alone could have significant effects on the outcome of a study. For example, in their meta-analysis of NMDA receptor modulators, Singh et al. demonstrated that sarcosine significantly improves negative symptoms when measured by the SANS, but not the negative subscale of the PANSS (Singh and Singh, 2011). Additionally, differences in various cognitive functions between elderly or chronically ill patients and patients experiencing their first episode of psychosis have been demonstrated and could have implications for medication intervention (Sponheim et al., 2010; Zanello et al., 2009).

Given the lack of biomarkers to measure treatment response, clinical trials must rely on instruments to measure symptoms and neuropsychological testing to measure cognitive function. While the MCCB, the current gold standard for cognitive testing in schizophrenia, has been shown to be reliable with minimal practice effects (Kern et al., 2008; Nuechterlein et al., 2008), it is still unknown whether or not the MCCB reflects improvement in cognition from pharmacologic treatment (Chou et al., 2013). The PANSS and SANS, the most commonly used instruments to measure negative symptoms in our review, are reliable instruments with good psychometric properties though they both have significant limitations that may limit progress in both clinical trials and the search for biomarkers. These limitations have been described elsewhere in more detail (Blanchard et al., 2011), but include concerns about certain domains assessing cognitive functions (e.g., “attention” on the SANS) as opposed to negative symptoms (Harvey et al., 2006; Sayers et al., 1996), failure to make the distinction between “anticipatory pleasure” and “consummatory pleasure” (Gard et al., 2007), and reliance on behavioral observations with little assessment of experiential states. The authors also highlight the impact of stigma (Corrigan, 2004), family issues (Hooley, 2007), cognitive function (Bellack et al., 1994), and socioeconomic stressors on domains such as social and emotional withdrawal (Blanchard et al., 2011). Notably, following the NIMH-MATRICS consensus statement on negative symptoms in 2006 (Kirkpatrick et al., 2006), which called for the development of rating instruments to address some of these limitations, researchers have developed two new assessment tools: the Clinical Assessment Interview for Negative Symptoms (CAINS) (Kring et al., 2013) and the Brief Negative Symptom Scale (BNSS) (Kirkpatrick et al., 2011), both of which demonstrate good psychometric properties (Horan et al., 2011; Kirkpatrick et al., 2011).

15. Theoretical issues

A significant theoretical concern in experimental clinical trials of schizophrenia is the assumption that the symptoms targeted are caused by a single underlying disorder with discrete biological underpinnings. The difficulty researchers have had in finding reliable biomarkers in schizophrenia is likely illustrative of the shortcomings of this assumption. Furthermore, there is a large amount of etiological hypotheses of schizophrenia with variable levels of evidence including genetic (Schizophrenia Working Group of the Psychiatric Genomics, 2014), neurodevelopmental (Fatemi and Folsom, 2009), inflammatory (Kirkpatrick and Miller, 2013), immune system disturbances (Eaton et al., 2006; Horvath and Mirnics, 2014; Sekar et al., 2016), trauma (Varese et al., 2012), and socioeconomic status (Werner et al., 2007), in addition to reported dysfunction in over twenty neurotransmitter and neuropeptide systems (Bernstein et al., 2005; Boison et al., 2012; Ferrier et al., 1983; Hagan et al., 1993; Heleniak and O'Desky, 1999; Howes and Kapur, 2009; Javitt and Zukin, 1991; Kulkarni et al., 2001; Leonard et al., 2002; Lewis et al., 2005; Marx et al., 2006; Morris et al., 2008; Notarangelo and Pocivavsek, 2017; Palha and Goodman, 2006; Rich and Caldwell, 2015; Schizophrenia Working Group of the Psychiatric Genomics, 2014; Schmauss and Emrich, 1985; Spooren et al., 2005; Vacic et al., 2011; Volk and Lewis, 2016; Yamamoto and Hornykiewicz, 2004), nearly all of which have been targeted by an experimental medication, as reviewed above. Though many of these systems are functionally related and likely not all of these hypotheses are completely relevant for treatment development, the many possible pathophysiological roads to the schizophrenia phenotype as currently defined point toward important considerations for clinical trial design and also suggest why so many molecules that succeed in animal models fail in human subjects.

Our current diagnostic criteria for schizophrenia, while reliable and clinically valuable, might be too broad for the purposes of clinical trials, as the subjects may be too heterogeneous in underlying pathophysiology. A simplified, yet potentially analogous, example is heart failure (HF). Patients with HF may appear phenotypically similar and share similar clusters of symptoms including shortness of breath, cough, and edema. However, the underlying pathophysiology could be ischemic, viral, autoimmune, nutritional, or rheumatologic, which has important implications for diagnosis, prognosis, and treatment. Thus, within a particular trial for schizophrenia, it is possible that a few patients may have responded significantly to serendipitously personalized treatment, but the effect would go unnoticed due to the lack of specificity for the other patients. Moreover, though negative symptom domains are correlated with one another, there is a strong possibility that each domain has a distinct underlying neurobiology with different responses to various medication. The same could be said for domains of positive symptoms such as hallucinations, delusions, and thought disorder. Thus, the use of sum scores in clinical trials, which has been shown to be problematic in major depression (Fried and Nesse, 2015), may obscure the response of a single symptom domain to a medication, increasing the chance of type II error.

Importantly, while we did not formally assess for publication bias, it should be noted that we cannot rule out publication bias, as nearly 10% of papers we reviewed were from a single group who reported positive trials in 23 out of 24 studies (Akhondzadeh et al., 1999, 2000, 2002, 2003, 2005, 2007, 2008a, 2008b, 2009, 2011; Farokhnia et al., 2013, 2014; Ghanizadeh et al., 2014; Hosseini et al., 2014; Iranpour et al., 2016; Khodaie-Ardakani et al., 2013, 2014, 2015; Modabbernia et al., 2013; Noorbala et al., 1999; Noroozian et al., 2013; Rezaei et al., 2013; Salimi et al., 2008; Zeinoddini et al., 2014).

16. Future directions

Based on the findings of this review, we propose several recommendations for future trials of experimental agents in schizophrenia. First, we must ensure that future trials are conducted appropriately. This includes parallel-group design, adequate sample sizes and reliable outcome measures to increase power, proper handling of missing data, and clearly defined outcome measures. Trials should be of adequate length (at least 12 weeks) particularly for negative and cognitive symptoms (Kemp et al., 2010; Kirkpatrick et al., 2001), which may take longer to improve than positive symptoms. It is important to continue studying factors associated with the placebo response in schizophrenia in order to minimize its effects (Kemp et al., 2010). We must continue the efforts to create reliable, data-driven, and biologically informed instruments such as the CAINS and BNSS, while also considering the importance of individual symptom domains. In an attempt to reduce heterogeneity, we should pursue the study of more homogenous patient sub-groups or stages of illness such as clinical high risk patients, patients experiencing their first episode of psychosis, or those suffering from the deficit syndrome, which has distinct features separating it from other forms of schizophrenia (Kirkpatrick et al., 2001). We should continue the search for biomarkers and endophenotypes to provide targets with better understood neural substrates and more objective markers of treatment response. For example, an imaging-based glutamate system marker could could have determined whether failed trials of pomaglumetad (Kinon et al., 2011) used inadequate doses to engage the glutamate system, or whether it may have failed despite engaging its target (i.e., mGluR 2/3). Finally, the numerous genes associated with schizophrenia provide a large and diverse array of molecular targets and effort must be expended to understand the biology of the implicated loci and genes (Schizophrenia Working Group of the Psychiatric Genomics, 2014). Choosing drug targets with human genetic evidence has been estimated to double the success rate in clinical drug development (Nelson et al., 2015). Though there are few clear targets to date, the identification of functionally relevant genetic loci such as the complement component 4 gene and SETD1A is beginning to point toward novel therapeutic pathways (Sekar et al., 2016; Singh et al., 2016). Combining well-designed clinical trials with careful patient selection and medications with strong biologic support is the most tractable way forward for the development of new treatments for schizophrenia. Ultimately, this approach forms the basis for personalized medicine which is beginning to transform other disciplines of medicine and will hopefully begin to impact psychiatry in the coming years.

Conflicts of interest

Dr. Girgis receives research support from Genentech, Otsuka, Forest/Allergan, and Bioadvantex. Dr. Zoghbi has no conflicts to disclose. Dr. Javitt has received grants from Roche, personal fees from Sunovion, Lundbeck, Envivo, Forum, Takeda, Autifony, Pfizer, and Glytech, and other fees from Glytech and NeuroRx. He also has two patents issued for D-serine in movement disorders and reduction in D-serine nephrotoxicity and a patent for D-cycloserine in depression licensed to NeuroRx. Dr. Lieberman serves on the advisory board of Intracellular Therapies and does not receive direct financial compensation or salary support for his participation; serves on the advisory board of Pierre-Fabre; receives grant support from Alkermes, Biomarin, Lilly, Psychogenics, EnVivo/Forum, Genentech, Novartis/Novation, and Sunovion; is a member of the advisory board of and holds financial interest in Clintara and Pear Therapeutics; and holds a patent from Repligen.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jpsychires.2018.07.006.

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