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Neuroprotective effects of the second generation antipsychotics

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ABSTRACT

Background: In contrast to over 30 studies reporting neurotoxicity associated with the first-generation antipsychotics (FGAs), several published studies have reported multiple neuroprotective effects associated with the second generation antipsychotics (SGAs). This prompted us to conduct a review of the reported neuroprotective mechanisms of the SGA class of antipsychotics compared to the FGAs.
Methods: A PubMed search was conducted using the keywords *antipsychotic*, *neuroprotection*, *neuroplasticity*, *neurogenesis*, *neurotoxicity*, *toxicity*, *brain volume*, *neuroinflammation*, *oxidative stress*, *myelin*, and *oligodendrocyte*. No restrictions were placed on the date of the articles or language. Studies with a clearly described methodology were included.
Results: Animal, cell culture, and human clinical studies were identified. Twenty-four reports met the criteria for the search. All studies included at least one SGA (aripiprazole, clozapine, lurasidone, olanzapine, paliperidone, perospirone, quetiapine, risperidone, and/or ziprasidone). A few also included FGAs as a comparator (predominantly haloperidol). All studies demonstrated at least one neuroprotective mechanism of one or more SGAs, while some studies also showed that FGAs ranged from having no neuroprotective effects to actually exerting neurotoxic effects leading to neuronal death.
Conclusions: A review of the literature suggests that in addition to their antipsychotic efficacy and low motoric side effects, SGAs exert measurable neuroprotective effects mediated via multiple molecular mechanisms and often in a dose-dependent manner. The neuroprotective effects of SGAs range from preventative to restorative and may play a salutary role in ameliorating the neurodegenerative effects of psychosis.

1. Introduction

The advent of second generation antipsychotics (SGAs) began with the introduction of clozapine in 1972 in Europe and later in 1988 in the U.S. (Crilly, 2007), and has since expanded to include a repertoire of 11 SGA agents. SGAs have been approved by the FDA to treat a variety of neuropsychiatric disorders, including schizophrenia, bipolar mania, bipolar depression, autism spectrum disorder, and as adjunctive therapy in treatment-resistant major depressive disorder. SGAs are also known as "atypical" antipsychotics due to their lower risk of acute extrapyramidal side effects (EPS) and tardive dyskinesia (TD) compared to first generation antipsychotics (FGAs) or "typical" antipsychotics (Farah, 2005). The reduced risk of EPS and TD of the SGAs are attributed to the stronger serotonin 5-HT2A receptor antagonism, compared to dopamine D2 receptor antagonism as well as faster dissociation from the dopamine D2 receptors (Seeman, 2002).

Recent research over the past two decades have demonstrated that in addition to treating the delusions and hallucinations of psychosis, SGAs have been reported to have several salutary neuroprotective effects while FGAs are associated with multiple neurotoxic effects (Nasrallah and Chen, 2017). We decided to review all the studies that reported neuroprotective effects of SGAs because so such overview is yet available. We also believe that this review may provide a neurobiological contrast between the FGA and the SGA classes, which is different from the absence of difference in all-cause discontinuation (i.e. effectiveness) that emanated from the CATIE study (Lieberman et al., 2005a, b).

2. Methods

This systematic review was performed in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) method, as shown in Fig. 1.

2.1. Search criteria

An online search was conducted using PubMed for available literature on SGA's neuroprotective effects, using the terms *antipsychotic*,

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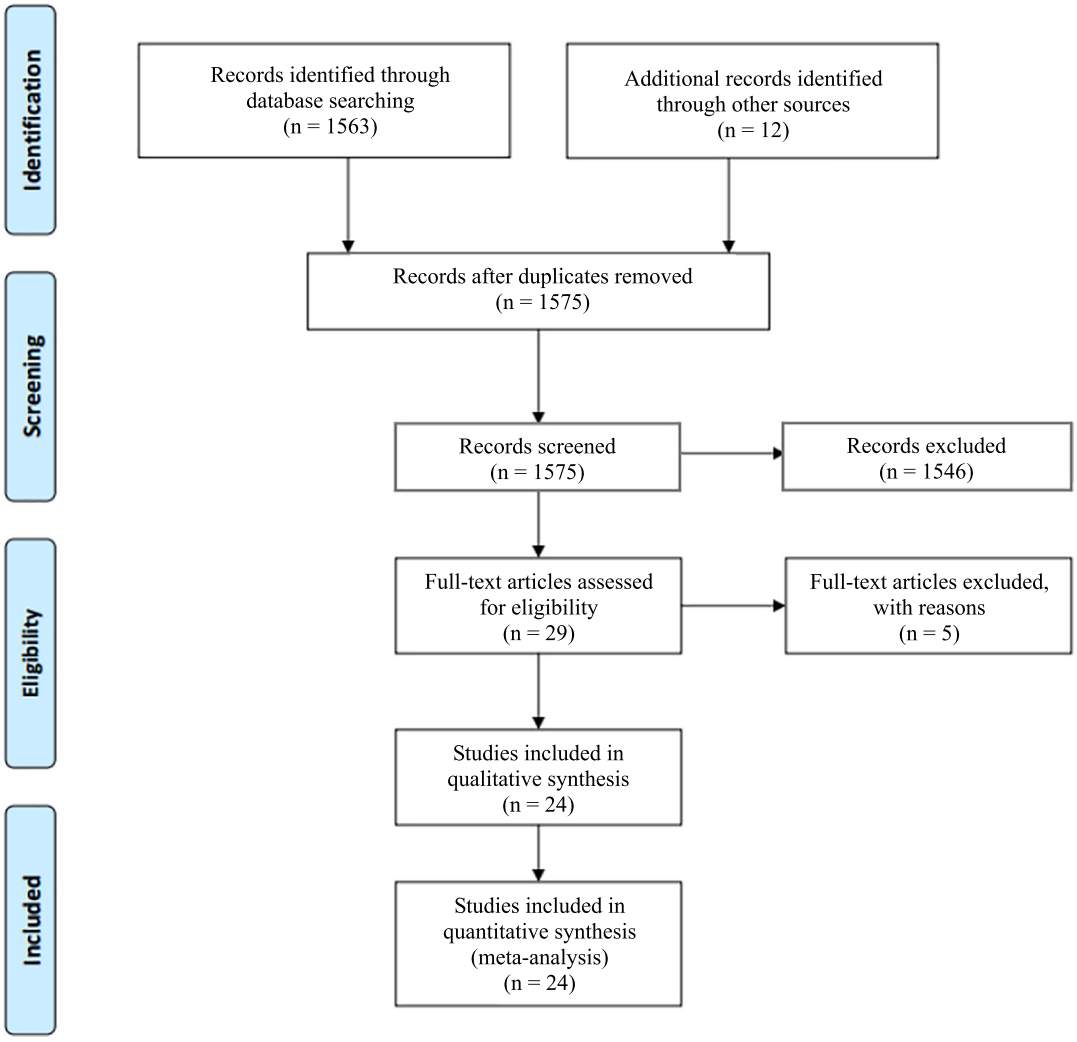

Fig. 1. Preferred reporting items for systematic reviews and meta-analysis 2009 flow diagram.

neuroprotection, *neuroplasticity*, *neurogenesis*, *neurotoxicity*, *toxicity*, *brain volume*, *oxidative stress*, *myelin*, and *oligodendrocyte*. There were no restrictions on the date of publication or language. The last database search was performed in July 2018.

2.2. Inclusion criteria

1. Studies that investigated neuroprotective effects of SGAs and/or their metabolites on neuronal cells, neural tissue, or white matter.
2. Studies based on animal models, cultured cell lines, or human studies.

2.3. Exclusion criteria

1. Studies that did not meet all inclusion criteria.
2. Studies in which the data were unclear and/or vague or employed questionable methodologies.

3. Results

3.1. Literature search

24 studies met our inclusion/exclusion criteria. Review articles were overall excluded if the trials included in those articles have already been included individually in our review. The studies were divided into three categories of in vitro preclinical studies, in vivo preclinical studies, and human clinical studies. The following is a chronological summary of the published findings of each report, highlighting the molecular mechanism of neuroprotection in each study. The chronological order depicts the evolution of data on the neuroprotective effects of SGAs. A few studies included more than one SGA and some of the studies also included data on FGA agents, such as haloperidol. The studies were categorized into 3 sections: In Vitro Preclinical Studies, In Vivo Preclinical Studies and Human Studies.

3.1.1. In vitro preclinical studies

3.1.1.1. Bian et al., 2008. In vitro administration atypical antipsychotics have significant anti-inflammatory effects in this mouse model through inhibition of microglial activation, suggesting possible benefits related to neurogenesis and decreasing neurotoxicity. Treatment of mouse 6–3 microglial cells with perospirone, quetiapine, and ziprasidone (5-30 μM) in conjunction with interferon-γ resulted in significantly decreased nitric oxide release from the activated microglia compared to controls, measured by the Griess assay, in a concentration dependent fashion ($P < 0.001$). In addition, treatment of the same cell line with perospirone and quetiapine in the presence of interferon-γ significantly inhibited TNF-α release in a concentration dependent manner ($P < 0.001$), while ziprasidone significantly increased TNF-α release ($P < 0.001$). No significance was found in nitric oxide or TNF-α release for cell lines treated with antipsychotics without the presence of

interferon-γ. No significant effects on cell viability were found with any of the three antipsychotics.

3.1.1.2. Park et al., 2009. In vitro treatment with aripiprazole offered neuroprotective effects with increasing BDNF, GSK-3β, and Bcl-2 levels in human dopaminergic neuroblastoma (SH-SY5Y). Cells were treated with either aripiprazole (5 μM or 10 μM) or haloperidol (5 μM or 10 μM) for 96 h of incubation and Western blot analysis was performed. The aripiprazole group had significantly increased BDNF promotor activity at a dose of 10 μM ($P < 0.01$) compared to controls and also significantly increased GSK-3β and Bcl-2 levels at both 5 μM ($P < 0.05$) and 10 μM ($P < 0.01$) doses. The haloperidol group did not have any significant differences in BDNF, GSK-3β, and Bcl-2 levels at either dosages compared to control.

3.1.1.3. Koprivica et al., 2011. In vitro aripiprazole protected embryonic cortical neurons from glutamate-induced neurotoxicity in a rat animal model utilizing 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide (MTT) and high-content nuclear condensation imaging assays. Pretreatment with aripiprazole (200 nM) significantly increased rat embryonic cortical neurons survival after exposure to glutamate in vitro ($P < 0.001$) in a concentration dependent manner (glutamate range 100–1000 μM). Olanzapine (1 μM) had significant protective effects only at glutamate exposure of 100 μM ($P < 0.05$), but not at 500 μM or 1000 μM, and risperidone (1 μM) had worse cell survival compared to control ($P < 0.01$) at 500 μM of glutamate. Addition of a selective serotonin $5HT_{1A}$ receptor antagonist (WAY-100635) did not have significant neuroprotection on its own and did not significantly change maximum neuroprotection value from aripiprazole. Addition of a selective dopamine D_2/D_3 receptor antagonist (nor (−) raclopride) had significant neuroprotection on its own ($P < 0.01$) and resulted in a significant additive increase of neuroprotection when co-administered with aripiprazole ($P < 0.001$). Aripiprazole did not have significant effects on p-Akt-Ser-473, p-GSK-3β-Ser-9, or PARP activity, suggesting that other mechanisms may be involved in its neuroprotective properties.

3.1.1.4. Yang and Lung, 2011. In vitro treatment with antipsychotics offered varying amounts of neuroprotective effects against oxidative stress induced cell death in human dopaminergic neuroblastoma (SH-SY5Y). Cells that were treated with haloperidol, risperidone, paliperidone, and olanzapine all demonstrated cytotoxic effects in a dose dependent manner (10 μM, 50 μM, 100 μM) after 24 h of incubation, with haloperidol having the most cytotoxicity, however all groups demonstrated recovery towards baseline 96 h after treatment, with paliperidone having the most robust recovery. Cells pre-incubated with olanzapine (10, 50, 100, 200 μM), paliperidone (10, 50, 100 μM), risperidone (10, 50, 100 μM), or haloperidol (10, 50, 100 μM) for 24 h were exposed to $Aβ_{23–35}$ (40 μM), MPP^+ (100 μM), or hydrogen peroxide (400 μM) to stimulate oxidative stress induced neurotoxicity. All antipsychotic treated groups demonstrated significant dose-dependent decrease in neuronal cell death compared to control when exposed to $Aβ_{23–35}$ ($P < 0.05$), with paliperidone requiring the least dosage for robust efficacy, olanzapine having the greatest efficacy at high dose, and haloperidol have decreasing efficacy with higher doses. All antipsychotic treated groups other than risperidone demonstrated significant dose-dependent decrease in neuronal cell death compared to control when exposed to MPP^+ ($P < 0.05$), with paliperidone requiring the least dosage for robust efficacy, olanzapine having the greatest efficacy at high dose, haloperidol have decreasing efficacy with higher doses, and risperidone only have significance at 50 μM but not at 10 μM or 100 μM. No antipsychotic treated groups other than paliperidone demonstrated significant decrease in neuronal cell death compared to control when exposed to hydrogen peroxide ($P < 0.01$).

3.1.1.5. Peng et al., 2013. In vitro paliperidone treatment had neuroprotective properties against MK-801 (NMDA receptor antagonist) induced neurotoxicity in a rat animal model. MK-801 administration was used to simulate schizophrenia in this animal model. Mouse embryonic prefrontal cortical neurons treated paliperidone in the presence of MK-801 for 48 h had a dose dependent protective effect in increasing cell viability compared to cells treated with MK-801 alone, with optimal dose being 100 μM of risperidone in the presence of 100 μM of MK-801 ($P < 0.01$). 25, 50, or 200 μM of risperidone in the presence 100 μM of MK-801 did not show significance, suggesting adequate dosing is necessary to invoke neuroprotection but excessive dosing diminishes neuroprotective properties. Paliperidone (25–200 μM) alone did not demonstrate consistent significant differences in neuronal cell count compared to control. Suggested mechanisms for paliperidone's neuroprotection include attenuating MK-801 induced elevation of free calcium concentration ($P < 0.01$), retarding MK-801 mediated inhibition of neurite outgrowth ($P < 0.01$), and reversing MK-801 induced decreases of gene expression and phosphorylation of Akt1 and GSK3β ($P < 0.01$).

3.1.1.6. Xu et al., 2014. In vitro quetiapine and clozapine treatment were protective against cuprizone mediated inhibition of oligodendrocyte progenitor cell (OPC) differentiation into mature oligodendrocytes in rat embryonic cortical neurons. Cuprizone (copper-chelating agent) was administered to simulate schizophrenia related inflammation and demyelination in this animal model. OPCs were treated with cuprizone (20 μM) and haloperidol (0.5 μM), olanzapine (1 μM), clozapine (1 μM), or quetiapine (1 μM) for 72 h then changed to antipsychotic only medium for 5 additional days. Clozapine or quetiapine treatment in the presence of cuprizone administration resulted in significantly greater ratio of $O4^+$ cells (marker for mature oligodendrocytes) to $NG2^+$ cells (marker for progenitor cells) compared to haldol + cuprizone, olanzapine + cuprizone, or cuprizone only groups ($P < 0.05$).

3.1.2. In vivo preclinical studies

3.1.2.1. Wakade et al., 2002. In vivo risperidone and olanzapine oral treatment were associated with proliferation of subventricular zone neurons in a rat animal model. Adult male Wistar rats were fed haloperidol (0.4 mg/kg/day), risperidone (0.5 mg/kg/day), or olanzapine (2 mg/kg/day) for 21 days. Risperidone and olanzapine treatment groups had significantly increased quantity of BrdU+ cells (immunohistochemical marker for cellular proliferation) in the subventricular zone compared to haldol and control groups ($P < 0.0038$). In contrast, no significance was found between the haldol and control goups in BrdU+ cells in subventricular zone and no significance was found between any of the antipsychotic treatment groups in BrdU+ cells in the hippocampus compared to control.

3.1.2.2. Bai et al., 2003. In vivo olanzapine and clozapine injections resulted in upregulated BDNF mRNA expression in rat hippocampus. Adult male Wistar rats were dosed with olanzapine (10 mg/kg/day), olanzapine (2.7 mg/kg/day), or haloperidol (1 mg/kg/day) via intraperitoneal injections for 28 days. Olanzapine and clozapine treatment groups had significant increases in BDNF mRNA expression in CA1, CA3, and the dentate gyrus regions compared to the control group ($P < 0.01$), while the haloperidol treatment group had significant decreases in BDNF mRNA expression in the CA1 ($P < 0.05$) and dentate gyrus ($P < 0.01$) regions compared to the control group.

3.1.2.3. Pillai et al., 2006. In vivo olanzapine and risperidone oral administration in rats resulted in less deleterious effects on neurotrophic factors in the brain compared to haloperidol and chlorpromazine, particularly for hippocampal BDNF levels. Adult male Wistar rats were dosed with either haloperidol 2 mg/kg/day, chlorpromazine 10 mg/kg/day, olanzapine 10 mg/kg/day, or risperidone 2.5 mg/kg/day. Rats that received olanzapine or risperidone for 90 days did not have significant changes in hippocampal BDNF levels compared to controls while the rats that received haloperidol or chlorpromazine for 90 days

did ($P < 0.05$). After 180 days of treatment, the haloperidol and chlorpromazine groups remained significantly decreased in BDNF levels compared to controls, the risperidone group became significantly decreased compared to controls but was still higher relatively to the FGAs ($P < 0.05$), and the olanzapine group continued to show no significant changes compared to controls. The study also showed that treatment with olanzapine or risperidone for 90 days after completing 90 days of treatment with haloperidol resulted in a significant restoration of hippocampal BDNF levels compared to control ($P < 0.05$). Striatal BDNF were significantly decreased in all treatment groups compared to control after both 90 days and 180 days ($P < 0.001$), however treatment with olanzapine or risperidone for 90 days after completing treatment with haloperidol for 90 days significantly restored striatal BDNF levels (with olanzapine $P < 0.001$ restoring more than risperidone $P < 0.05$). All treatment groups had significantly decreased NGF levels in both hippocampus and striatum after both 90 days and 180 days ($P < 0.05$). Treatment with olanzapine or risperidone for 90 days after completing treatment with haloperidol for 90 days significantly restored hippocampal and striatal NGF levels ($P < 0.05$).

3.1.2.4. Yulug et al., 2006. In vivo treatment with risperidone decreased brain damage sustained after cerebral ischemic in this mouse animal model. Adult male C57BL/6j mice underwent intraluminal filament technique to produce permanent occlusion of the middle cerebral artery and were treated with risperidone (0.1 mg/kg, 1 mg/kg, or 10 mg/kg) via intraperitoneal injection right after procedure, then sacrificed 24 h post treatment for analysis. Mice treated with risperidone at all doses showed significantly smaller infarct volume compared to the vehicle group ($P < 0.05$).

3.1.2.5. Wang and Deutch, 2008. In vivo chronic treatment with olanzapine but not haloperidol reversed 6-OHDA induced changes in the prefrontal cortical pyramidal cell dendrites. Adult male Sprague-Dawley rats were treated with 6-OHDA to induce bilateral ventral tegmental area lesions to simulate schizophrenia related dendritic changes through neurotoxic destruction of dopaminergic and noradrenergic neurons. 6-OHDA treated groups demonstrated a significant decrease in dendritic length and dendritic spine density in the prefrontal cortex compared to controls ($P < 0.001$). Rats that were treated for 3 weeks with olanzapine (7.5 mg/kg/day) via drinking water after receiving the 6-OHDA induced lesions 3 weeks prior resulted in reversal of the dendritic damages caused by the neurotoxic lesions (no significant changes compared to control group), while rats that were treated for 3 weeks with haloperidol (2.0 mg/kg/day) via drinking water still had significant loss of dendritic length and dendritic spines compared to control ($P < 0.001$).

3.1.2.6. Xiao et al., 2008. In vivo quetiapine oral administration was neuroprotective in ameliorating cuprizone induced myelin breakdown in a mouse animal model. Cuprizone (copper-chelating agent) was administered to simulate schizophrenia related inflammation and demyelination in this animal model. Adult male C57BL/6 mice were treated with quetiapine for 5 weeks (10 mg/kg/day) and exposed to cuprizone (0.2%, *w*/w) during weeks 2–5. The quetiapine+cuprizone treatment group had significantly less myelin breakdown compared to the cuprizone only group ($P < 0.05$), but still had significant losses compared to the control group ($P < 0.01$). Quetiapine alone in the absence of prior cuprizone administration did not demonstrate significant differences in myelination compared to the control group.

3.1.2.7. Nasrallah et al., 2010. In vivo paliperidone oral administration was correlated with significantly increased neuronal proliferation in the olfactory epithelium and in the neurogenic subventricular zone in rats, suggesting possible neurogenerative effects. Adult male Sprague-Dawley rats that received paliperidone (1 mg/kg/day) and risperidone (1 mg/kg/day) for 28 days via water consumption had significantly increased olfactory epithelium cell counts (labeled by BrdU+) compared to controls ($P < 0.005$). Rats that received paliperidone (0.6 mg/kg/day) for 28 days also had significantly elevated neurogenesis in the olfactory epithelium and subventricular zones compared to the control group ($P < 0.05$), but rats that received risperidone (0.6 mg/kg/day) did not. Neither paliperidone (0.6 mg/kg/day) nor risperidone (0.6 mg/kg/day) significantly increased the hippocampal dentate gyrus cell count compared to control. Unclear cause for inconsistent cellular proliferation in response to risperidone, differing doses of administration might have been a factor. Another possibility is that the hydroxylation of risperidone into paliperidone [9-hydroxy risperidone] may exert a neuroprotective effect compared to the mother molecule.

3.1.2.8. Elsworth et al., 2011. In vivo olanzapine treatment in phencyclidine exposed mouse model had protective effects against asymmetric spine synapses in layer II/III of prefrontal cortex, suggesting possible benefits in improving neuroplasticity in schizophrenia. Subchronic phencyclidine treatment was utilized to simulate schizophrenia-like neurological insult in this animal model. Adult male Sprague-Dawley rats that received 7 days of intraperitoneal injections of 5 mg/kg phencyclidine hydrochloride and subsequently treated with olanzapine demonstrated significant reductions in loss of asymmetric spine synapses in layers II/III of the pre-frontal cortex compared to controls. The reversal effects were significant in both acute treatment (one time dose of 1.5 mg/kg intraperitoneal 1 week after phencyclidine withdrawal, $P < 0.001$) and chronic treatment (8.4 kg/mg average daily intraperitoneal dose over 21 days starting 1 week after phencyclidine withdrawal, $P < 0.0001$) with olanzapine. Both acute and chronic olanzapine treatment in the absence of phencyclidine exposure did not result in significant differences in asymmetric spine synapse density compared to control groups.

3.1.2.9. Fumagalli et al., 2012. In vivo lurasidone treatment via oral administration increased BDNF expression in the prefrontal cortex and hippocampus in this rat animal model. Adult male Sprague-Dawley rats were administered lurasidone (10 mg/kg/day) for 21 days via oral gavage. Additionally, a portion of the rats in both the lurasidone and control groups were exposed to acute stress in the form of a 5 min forced swim stress 24 h after the last treatment administration. BDNF mRNA levels were significantly increased in the prefrontal cortex of rats in both the lurasidone treatment group and the lurasidone+stress group compared to controls ($P < 0.01$). BDNF mRNA levels were significantly increased in the hippocampus only in the lurasidone+stress group ($P < 0.05$) and not the lurasidone only group compared to controls. Acute stress alone was not significant in increasing BDNF mRNA levels compared to controls in either the prefrontal cortex or the hippocampus.

3.1.2.10. Stojkovic et al., 2012. In vivo risperidone treatment via oral administration had benefits in restoring antioxidant defense alterations induced by PCP treated rats. Male Wistar rats were treated with phencyclidine (10 mg/kg) at 2, 4, 6, 9, and 12 days after birth to simulate schizophrenia in this animal model. Phencyclidine treated rats that subsequently received risperidone (0.84 mg/kg/day) for 9 weeks had significantly higher levels of glutathione in the brain cortex and hippocampus compared to the phencyclidine only group ($P < 0.05$). The risperidone+phencyclidine group also had higher levels of γ-glutamate cysteine ligase activity, higher levels of glutathione peroxidase activity, higher levels of glutathione reductase activity, and lower levels of lipid peroxidation than the phencyclidine only group ($P < 0.05$).

3.1.2.11. Zhang et al., 2012. In vivo quetiapine treatment restored cuprizone induced myelin and oligodendrocyte loss in a mouse animal model. Cuprizone (copper-chelating agent) was administered to simulate schizophrenia related inflammation and demyelination in this

mice animal model. Male C57BL/6 mice were orally fed cuprizone (0.2%, *w*/w) for 12 weeks and then treated with quetiapine (10 mg/kg/day) via oral administration for 2, 3, or 4 weeks. The quetiapine treatment group had significantly greater increase in MBP, GST-Pi, and olig2 cells (markers of mature oligodendrocytes and remyelination) in the frontal cortical and corpus callosum neurons compared to vehicle ($P < 0.01$) at all time points.

3.1.2.12. Yan et al., 2014. In vivo treatment with risperidone decreased brain damage sustained after cerebral ischemic in this mouse animal model. Adult Male Sprague-Dawley rats underwent transient focal cerebral ischemia after occluding the right middle cerebral artery for 2 h using a monofilament nylon suture. The rats were treated with risperidone pre- and post-procedure (2 mg/kg or 4 mg/kg) and then sacrificed 2 days after the procedure for analysis. Rats treated with risperidone 4 mg/kg pre- and post-procedure had significantly less infarct volume compared to the vehicle and risperidone 2 mg/kg group ($P < 0.05$).

3.1.2.13. Zhang et al., 2014. In vivo olanzapine protected against cuprizone induced myelin and oligodendrocyte loss in a mouse animal model. Cuprizone (copper-chelating agent) was administered to simulate schizophrenia related inflammation and demyelination in this animal model. Female C57BL/6 mice were treated with quetiapine (10 mg/kg/day) via oral route for 6 weeks and administered cuprizone (0.2%, *w*/w) for weeks 2–6. Olanzapine + cuprizone group had significantly higher levels of MBP in frontal cortical neurons and higher levels of IGF-1 mRNA compared to cuzprizone only group ($P < 0.01$).

3.1.2.14. Martin et al., 2015. In vivo olanzapine treatment significantly reversed genetic alterations induced by phencyclidine in a monkey animal model. Phencyclidine administration was used to simulate schizophrenia in this animal model. Cynomolgus monkeys that were administered phencyclidine (1 mg/kg/day) via osmotic pump implant for 2 weeks then treated with oral olanzapine (0.75 mg/kg/twice daily) in conjunction with phencyclidine administration (2 mg/kg/day) via osmotic pump implant for 4 weeks showed normalization of a significant portion of gene-transcript alterations induced by phencyclidine when analyzed using microarrays (Affymetrix HU6800 and HG-U95A/HG-U95Av2). Canonical pathways analysis (utilizing Ingenuity Pathways Analysis software) identified significant overrepresentation of genes implicated in genetic disorders, including schizophrenia, neurological disorders, and cell death amongst the genes normalized by olanzapine administration. Gene changes associated with olanzapine treatment were seen predominantly in correlation with phencyclidine exposed subjects and olanzapine administration alone without phencyclidine exposure resulted in minimal gene alterations comparatively.

3.1.2.15. Shao et al., 2015. In vivo quetiapine protected against cuprizone mediated oligodendrocyte losses, astrocyte and microglia activation, and TNF-α and IL-6 increases in a mouse animal model. Cuprizone (copper-chelating agent) was administered to simulate schizophrenia related inflammation and demyelination in this animal model. Male C57BL/6 mice were treated with quetiapine (10 mg/kg/day) via intraperitoneal injection for 2 weeks and administered cuprizone (0.2%, *w*/w) starting in the second week. Brain tissue analysis after the 2 weeks demonstrated that mice treated with quetiapine+cuprizone had significantly lower levels of activated astrocytes and microglia compared to normal saline + cuzprizone group ($P < 0.01$), had significantly lower levels of TNF-α and IL-6 ($P < 0.05$), and had significantly less oligodendrocyte loss ($P < 0.05$). Quetiapine only group did not have significant differences in oligodendrocyte losses, astrocyte and microglia activation, and TNF-α and IL-6 compared to control group. Normal saline +cuprizone group demonstrated significantly increased oligodendrocyte losses ($P < 0.01$), astrocyte and microglia activation ($P < 0.01$), and TNF-α and IL-6 increases ($P < 0.05$) compared to control group.

3.1.3. Human clinical studies

3.1.3.1. Lieberman et al., 2005a. In vivo olanzapine treatment was associated with preservation of brain volume in first episode psychosis human subjects compared to haloperidol. Subjects with DSM-IV diagnosis of schizophrenia, schizophreniform, or schizoaffective disorder experiencing first episode psychosis were treated with either olanzapine (5–20 mg daily) or haloperidol (2–20 mg daily). The haloperidol treatment group had significantly decreased whole brain grey matter compared with controls at 12 weeks ($P < 0.005$) and at 52 weeks ($P < 0.001$), while the olanzapine treatment groups did not have significant brain volume changes from control. The decrease in grey matter in the haloperidol treatment group remained significant with specific individual lobes that where analyzed at 52 weeks, including the frontal lobe ($P < 0.001$), temporal lobe ($P = 0.03$), and the parietal lobe ($P = 0.002$).

3.1.3.2. Pedrini et al., 2011. In vivo chronic clozapine treatment was positively associated with an increase in serum BDNF levels in a dose dependent manner in human subjects diagnosed with schizophrenia (per DSM-IV criteria). All subjects were recruited from outpatient clinic and none of them had any neurological disease, brain tumor, thyroid disease, severe hepatic disease, severe cardiac disease or any other psychiatric diagnosis. Serum BDNF levels were measured with ELISA and found to have a significant positive correlation with clozapine daily dose ($P = 0.028$) but not with typical antipsychotic (haloperidol primary treatment with chlorpromazine augmentation as needed) daily dose.

3.1.3.3. Vita et al., 2015. Second generation antipsychotics were associated with preservation of brain volume in subjects with schizophrenia compared to first generation antipsychotics. A meta-analysis was performed that analyzed studies involving longitudinal magnetic resonance imaging studies of subjects with schizophrenia (per DSM III-R, DSM-IV, DSM-IV-TR, or ICD 10 criteria) that were being treated with antipsychotics (varied, did not specify which specific antipsychotics and only divided based on first vs second generation). The study found that there was a significant loss of whole brain, frontal lobe, temporal lobe, and parietal lobe grey matter in patients treated with first generation antipsychotics or a combination of first generation and second generation antipsychotics compared to controls ($P < 0.001$). However, there was no significant whole brain or lobe specific grey matter loss in subjects that received only second generation antipsychotics compared to controls and there was conversely a non-significant trend towards increased grey matter volume compared to controls in the frontal and temporal lobes.

4. Discussion

This review of the published literature demonstrates that SGAs are associated with multiple neuroprotective effects. The mechanisms by which SGAs confer neuroprotection include a wide range from neurogenesis to protection against toxicity, ischemia or insults and increasing the odds of neuronal survival and neural tissue integrity. The SGAs investigated in the various studies and their mechanisms of neuroprotection are summarized in Table 1. One of the major proposed mechanisms by which SGAs exert their neuroprotective effects is the modulation of oxidative stress. Multiple SGAs including risperidone, paliperidone, olanzapine, quetiapine, and ziprasidone demonstrated benefits in decreasing oxidative stress through mechanisms such as reducing reactive oxygen species (ROS) formation and increasing oxidative protective factors, including glutathione and superoxide dismutase, leading to protection against apoptosis and myelin/oligodendrocyte loss (Bian et al., 2008; Xiao et al., 2008; Yang and Lung, 2011; Zhang et al., 2012; Stojkovic et al., 2012; Zhang et al., 2014; Xu et al., 2014; Shao et al., 2015). Another common proposed mechanism for SGAs' neuroprotective qualities is upregulation of neurotrophic

Table 1
SGAs included and their proposed mechanisms of neuroprotection.

SGAs represented in included studies
Aripiprazole
Clozapine
Lurasidone
Olanzapine
Paliperidone
Perospirone
Quetiapine
Risperidone
Ziprasidone
SGA mechanisms of neuroprotection
Attenuate brain damage after ischemic stroke
Decrease TNF-α and nitric oxide release in the presence of interferon-γ
Increase BDNF
Increase NGF
Increase oligodendrocyte regeneration and myelin repair
Increase OPC differentiation into mature oligodendrocytes
Neurogenesis
Prevent cortical grey matter loss
Prevent myelin breakdown and oligodendrocyte loss
Protect against cell death related to NMDA receptor dysfunction
Protect against glutamate toxicity
Protect against oxidative stress
Reverse altered/weakened antioxidant defense
Reverse dendritic changes

factors such as BDNF and NGF, primarily in the prefrontal cortex (Pillai et al., 2006; Park et al., 2009; Pedrini et al., 2011; Fumagalli et al., 2012). The increased neurotrophic factors would, in theory, activate downstream signaling pathways including PI3K/Akt with subsequent increase in Bcl-2, exerting anti-apoptotic action and enhancing neuronal survival (Wang et al., 2006). The increase in neurotrophic factors is observed only with SGAs and not FGAs like haloperidol (Pillai et al., 2006) possibly due to the $5HT_{2A}$ antagonism that is found in SGAs but not FGAs (Vaidya et al., 1997). The increase in neurotrophic factor with SGA treatment is consistent with multiple studies that demonstrate an increase neuroplasticity and neurogenesis as well, with repair of dendritic spine changes (Wang and Deutch, 2008; Elsworth et al., 2011), increased proliferation of subventricular zone neurons (Wakade et al., 2002; Nasrallah et al., 2010), and preservation of brain volume in schizophrenia subjects (Lieberman et al. 2005, Vita et al., 2015). These changes are possibly attributed to SGAs anti-serotonergic effects of increasing dopamine tone in mesocortical pathway by diminishing the inhibition of tonal dopamine via $5HT_{2A}$ antagonism (Egerton et al., 2008). Much of the proposed mechanisms described in the studies remains theoretical at this time and further clinical studies are needed to explore the etiology behind the neuroprotective benefits observed with SGAs.

The extent of SGAs neuroprotection appears to be generally dose-dependent with more neuroprotection at higher doses. However, there were a few exceptions such as with risperidone, where moderate doses were associated with greater neuroprotection than either lower or higher doses. The mechanism by which this phenomenon occurs remains unclear, but one possible theory might be related to risperidone's strong affinity for D2 receptors. Given that current evidence suggest that there is significant neurotoxicity associated with FGAs, especially haloperidol, perhaps higher doses of risperidone lead to excessive D2 blockade approaching that of the FGAs, which may trigger neurotoxic pathways, leading to decreased neuroprotective effects. This remains speculative at this time as there are limited human clinical trial data currently available and further studies are still needed to elucidate the optimal dosing to achieve maximal neuroprotection as well as the pharmacodynamics involved.

The current data are supportive of utilizing SGAs as first-line treatment options over FGAs given their neuroprotective profiles. Studies such as Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) (Lieberman et al., 2005b) and Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUTLASS) (Jones et al., 2006) have found that SGAs and FGAs have comparable clinical effectiveness but did not investigate any differential neuroprotective or neurotoxic effects across the first and second generation antipsychotics. Given that patients with active psychosis experience progressive brain-tissue degeneration as part of the pathophysiology of the disease (Cahn et al., 2002), serious consideration should be given to selecting a medication that may have neuroprotective benefits in minimizing brain tissue degeneration in this vulnerable population with serious neurobiological disorders.

Limitations of this study include the possibility that some of the animal model and cell culture studies may not necessarily be generalizable to humans. However, the totality of the evidence from cell cultures, animal models, and human neuronal tissue appears to be consistent.

The studies included in this review that received funding from industry sources are listed in Table 2.

Table 2
Studies that included industry funding support and their sources.

Study	Industry funding source
Lieberman et al., 2005a, b	Lilly Research Laboratories
Pillai et al., 2006	Janssen Pharmaceutica Research Foundation and Eli Lilly and Company
Wang and Deutch, 2008	Eli Lilly and Company
Nasrallah et al., 2010	Ortho McNeil Janssen Scientific Affairs LLC (OMJSA)
Fumagalli et al., 2012	Dainippon Sumitono Pharma Co. Ltd./Sunovion Pharmaceuticals Inc.
Martin et al., 2015	Eli Lilly and Company

5. Conclusion

Based on our review of the current literature, SGAs are associated with multiple neuroprotective properties via 14 different molecular mechanisms, ranging from neurogenesis to protection against neurotoxicity or insults and minimizing neuronal cell death. Due to the favorable benefits in attenuating neurodegeneration associated with psychosis in addition to their established efficacy in treating psychosis with decreased risk of EPS and TD, SGAs should be considered as the preferred first-line antipsychotic therapy Further controlled studies of the neuroprotective effects of SGAs are warranted to establish a rational algorithm for the clinical selection of antipsychotics for use in schizophrenia and related psychotic disorders.

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Contributors

Dr. Alexander Chen – performed literature search, reviewed articles and data, drafted manuscript, created tables and figures.

Dr. Henry Nasrallah – conceived the study and its design, reviewed articles and data, edited manuscript, edited tables and figures.

All authors contributed to and approved the final manuscript.

Conflict of interest

Dr. Alexander Chen reports none. Dr. Henry Nasrallah is a consultant to Acadia, Alkermes, Janssen, Sunovion, Lundbeck, Indivior, Otsuka, Teva, Neurocrine; is a speaker for Acadia, Alkermes, Allergan, Janssen, Otsuka, Sunovion; no stock ownership in any company.

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