Journal of Cytology & Histology
ISSN: 2157-7099

Werner and Covenas, J Cytol Histol 2016, 7:4
DOI: 10.4172/2157-7099.1000441

Review Article · Open Access

Current Treatment of Schizoaffective Disorder According to a Neural Network

Felix-Martin Werner[1,2*] and Rafael Covenas[2]

[1]*Höhere Berufsfachschule für Altenpflege und Ergotherapie der Euro Akademie Pößneck, Pößneck, Germany*
[2]*Institute of Neurosciences of Castilla y León (INCYL), Laboratory of Neuroanatomy of the Peptidergic Systems (Lab. 14), University of Salamanca, Salamanca, Spain*

Abstract

Schizoaffective disorder, which is combined with schizophrenic and affective, i.e. depressive or manic or alternating depressive and manic symptoms, has a prevalance of 0.5%. Here, we describe the alterations of the most important classical neurotransmitters in the brain regions involved in schizophrenic and affective symptoms. Schizoaffective is undoubtedly an inheritable chronic psychiatric disease, whereby traumata can enhance schizophrenic and affective symptoms in one third of patients. Neural networks are described in the brainstem, hippocampus and ventral tegmental area and the mentioned neurotransmitter alterations are considered. Prophylactic treatment of schizoaffective patients consists of administering mostly second-generation antipsychotic drugs alone or in combination with mood-stabilizing drugs. The clinical importance of the antipsychotic drug clozapine for a pharmacotherapy of treatment-resistant forms of the disease is underlined.

Keywords: Clozapine; Dopamine; Extrapyramidal symptoms; GABA; Glutamate; Lithium; Mood-stabilizing drug; Noradrenaline; Olanzapine; Quetiapine; Risperidone; Second-generation antipsychotic drug; Serotonin

Introduction

While schizophrenia, a chronic disabling psychiatric disease, affects 1% of the population, schizoaffective disorder has a prevalance of 0.5%. Schizoaffective patients show positive schizophrenic symptoms (paranoia, hallucinations, illusions), negative schizophrenic symptoms (social withdrawal, autism, mutism) and cognitive deficits. Schizophrenic symptoms are combined with affective, i.e. depressive, manic or bipolar symptoms. Schizoaffective disorder becomes manifest as an acute psychosis with mostly positive schizophrenic and depressive or manic symptoms [1-3]. The brain regions involved in schizophrenic symptoms are the hippocampus, the prefrontal cortex and the ventral tegmental area. In these brain regions, dopamine hyperactivity via D_2 receptors and serotonin hyperactivity via 5-HT_{2A} receptors occur. Besides, an hypoactivity of presynaptic inhibitory neurons, namely GABAergic neurons via $GABA_A$ receptors and glutamatergic neurons via NMDA (N-methyl-D-aspartate) neurons, has been reported. Dopamine hyperactivity and GABA and glutamate dysfunction is encoded by the susceptibility genes of the schizophrenic symptoms [4]. The brain regions involved in affective symptoms are the hippocampus and the brainstem. In these brain regions, hypoactivity of monamines, namely noradrenaline, serotonin and dopamine neurons and hyperactivity of presynaptic inhibitory neurons, i.e. GABAergic and glutamatergic neurons can be found [5,6]. 30% of the schizoaffective patients experienced traumata and this enhanced the disease symptoms [7]. Schizoaffective disorder is treated generally with second-generation antipsychotic drugs such as risperidone, olanzapine, quetiapine or aripiprazole. The antipsychotic drugs are mostly D_2 and 5-HT_{2A} antagonists and improve positive and negative schizophrenic symptoms [8]. Additionaly, mood-stabilizing drugs such as lithium, carbamazepine or lamotrigine can be administered in order to prevent recurrence of psychotic or affective symptoms [9].

Alterations of Classical Neurotransmitters and Neuropeptides in the Brain Regions Involved in Schizophrenic Symptoms

The brain regions involved in schizophrenic symptoms are the hippocampus, the prefrontal cortex and the ventral tegmental area [3]. After the description of some susceptibility genes related with the schizophrenic symptoms and the coherence between genetic localization and cellular mechanisms [10], a multi-neurotransmitter system has been also described in the above mentioned brain regions. In the ventral tegmental area, dopamine hyperactivity via D_2 receptors and serotonin hyperactivity via 5-HT_{2A} receptors have been described, while dopamine hyperactivity was due to a reduced activity of the enzymes degrading dopamine, namely COMT (catechol-O-methyl transferase) and monamine oxidase. Presynaptic inhibitory neurons are also important and it is known that GABA hypoactivity, via $GABA_A$ receptors, is encoded in the GAD (glutamic acid decarboxylase)-67 gene and glutamate hypoactivity, via NMDA receptors, in the dysbindin-1 and neuregulin-1 genes [11]. Some neuropeptides are also involved in psychotic symptoms, for example in the prefrontal cortex, decreased levels of cholecystokinin and neurotensin have been reported [12].

Dopamine

In schizophrenia and in the schizoaffective disorder, a dopamine hyperactivity via D_2 receptors has been described in the hippocampus, the prefrontal cortex and the ventral tegmental area. Dopamine hyperactivity is enhanced by a reduced activity of two enzymes degrading dopamine, namely COMT and monoamine oxidase [12]. In the section about the neural networks, it will be pointed that in the ventral tegmental area GABAergic neurons, due to the gene GAD 67, exert a weak presynaptic inhibitory action on D_2 dopaminergic neurons and enhance dopamine hyperactivity. Although the antipsychotic drug

***Corresponding author:** Felix-Martin Werner, Instituto de Neurociencias de Castilla y León (INCYL), Laboratorio de Neuroanatomía de los Sistemas Peptidérgicos (Lab.14) c/Pintor Fernando Gallego, 137007-Salamanca, Spain, Tel: +34/923/29 1856; Fax: +34/923/29 45 49; E-mail: felixm-werner@versanet.de

Received September 28, 2016; **Accepted** December 02, 2017; **Published** December 10, 2017

Citation: Werner FM, Covenas R (2016) Current Treatment of Schizoaffective Disorder According to a Neural Network. J Cytol Histol 7: 441. doi: 10.4172/2157-7099.1000441

clozapine (a D_3, D_4 and 5-HT_{2A} antagonist) exerts an antipsychotic effect higher to other antipsychotic drugs, the D_2 antagonistic effect is of great importance in the treatment of schizophrenic symptoms [13].

Serotonin

Serotonin hyperactivity via 5-HT_{2A} receptors can be found in the hippocampus and the ventral tegmental area. In animal experiments, NMDA receptor antagonists, for example MK-801 can induce schizophrenia-like behavior which can be relieved by risperidone, a D_2 and 5-HT_{2A} antagonist and ritanserin, a 5-HT_{2A} and 5-HT_{2C} receptor antagonist, but not by haloperidol, a D_2 antagonist [14]. In the section about neural networks, it will be pointed out that glutaminergic neurons exert a reduced presynaptic inhibitory function, via NMDA receptor, on 5-HT_{2A} serotonergic neurons in the hippocampus and ventral tegmental area and enhance serotonin hyperactivity [3].

Gamma-aminobutyric acid (GABA)

GABA is a presynaptic inhibitory neurotransmitter, which exerts its function via $GABA_A$ and $GABA_B$ receptors. In schizophrenic and schizoaffective patients, GABA is dysfunctional in the hippocampus, prefrontal cortex and ventral tegmental [15]. In these brain regions, it has been reported reduced levels of GAD 67 mRNA and GAD protein in the prefrontal cortex of schizophrenic patients [16]. GABAergic neurons could enhance D_2 dopamine hyperactivity through a decreased presynaptic inhibition via $GABA_A$ receptors [12].

Glutamate

Glutamate is dysfunctional in the brain regions in schizophrenic brain regions due to the susceptibility genes dysbindin-1 and neuregulin-1, which encode glutamate hypoactivity via the NMDA receptor in the prefrontal cortex, hippocampus and ventral tegmental area. It has been examined whether a positive allosteric modulator at the NMDA receptor might be of therapeutic effec in schizophrenia and schizoaffective disorder [17].

Alterations of Classical Neurotransmitters and Neuropeptides in the Brain Regions Involved in Affective Symptoms

Schizoaffective patients show schizophrenic symptoms accompanied by affective symptoms, i.e. depressant, manic or bipolar, alternating depressant and manic symptoms. The brain regions involved in the affective symptoms are the brainstem and hippocampus. In patients showing depressive symptoms, hypoactivity of monoamines, i.e. of dopamine, noradrenaline and serotonin can be found respectively in the brainstem and hippocampus. In addition to the hypoactivity of these postsynaptic excitatory neurotransmitters, hyperactivity of the presynaptic inhibitory neurotransmitters GABA and glutamate can be found. In patiens showing manic symptoms, hyperactivity of dopamine and serotonin and hypoactivity of the presynaptic inhibitory neurotransmitters GABA and glutamate occurs. A neural network will be developed in order to explain the interactions between these neuroactive substances in a multi-neurotransmitter system (Figure 1) [12].

Noradrenaline

In depressive and manic symptoms, noradrenaline alterations are of importance in the midbrain and hippocampus. In depressive patients, hypoactivity of noradrenaline via alpha1 receptors is partly due to polymorphisms of the noradrenaline transporter gene. Patients with polymorphisms of this gene better respond to selective noradrenaline and serotonin reuptake inhibitors than to selective serotonin reuptake inhibitors [18].

Serotonin

Serotonin hypoactivity in the brainstem and hippocampus can be found in depressive patients; this serotonin alteration is partly due to polymorphisms of the sertonin transporter gene. Selective serotonin reuptake inhibitors improve depressive symptoms; this effect being combined with an antagonism at other serotonergic receptors, namely 5-HT_{2C} and 5-HT_7 receptors [19].

Dopamine

In the hippocampus, dopamine shows hypoactivity in schizodepressive patients and hyperactivity in schizomanic patients. In depressive patients, the selective dopamine and noradrenaline reuptake inhibitor bupropion improves the decreased positive effect, i.e. the loss of interest, pleasure and interest. However, in schizodepressive patients, the antidepressant drug bupropion should not be administered, because bupropion can enhance dopamine hyperactivity and worsen manic or schizophrenic symptoms, when they occur.

Gamma-aminobutyric acid (GABA)

GABA shows dysfunction in depressive and manic symptoms in the brainstem and hippocampus. In the brainstem, GABAergic neurons strongly presynaptically inhibit alpha1 noradrenergic neurons, via $GABA_B$ receptors, and contribute to noradrenaline hyperactivity in depressive symptoms [20,21]. In schizomanic patients, in the hippocampus, GABAergic neurons weakly presynaptically inhibit D_2 dopaminergic neurons via $GABA_A$ receptors [4].

Glutamate

In schizodepressive and schizomanic patients, glutamate shows respectively hypo- and hyper-activity in the brainstem and hippocampus. In the brainstem, glutamatergic neurons strongly presynaptically inhibit 5-HT_{1A} serotonergic neurons via subtype 5 of metabotropic glutamatergic receptors (m5GluRs) and enhance serotonin hypoactivity [12]. NMDA receptor and m5Glu receptor antagonists exert an antidepressant effect. However, in schizodepressive patients, these novel antidepressant drugs should not be administered, because in the hippocampus and ventral tegmental area, an antagonism at the NMDA receptor could enhance 5-HT_{2A} serotonin hyperactivity through a reduced presynaptic inhibition, enhancing psychotic symptoms [22].

Neural Networks in the Brain Regions Involved in Schizophrenic and Affective Symptoms

Neural networks in the brainstem, hippocampus and ventral tegmental area can be described as follows: In the brainstem, alpha1 noradrenergic neurons, originating from the locus coeruleus activate glutamatergic neurons, which inhibit 5-HT_{1A} serotonergic neurons from the medial raphe nucleus, via NMDA receptors. The latter neurons activate GABAergic neurons, which inhibit alpha1 noradrenergic neurons via $GABA_A$ receptors. This neural circuit is located in the center of the circadian rhythm; in this circuit, alternating levels of the activating neurotransmitter noradrenaline and the soothing neurotransmitter serotonin influence each other. Noradrenaline is preponderant during the day and serotonin during the night (Werner and Coveñas). Alpha1 noradrenergic neurons activate glutamatergic neurons which inhibit 5-HT_{1A} serotonergic neurons from the dorsal raphe nucleus via 5Glu

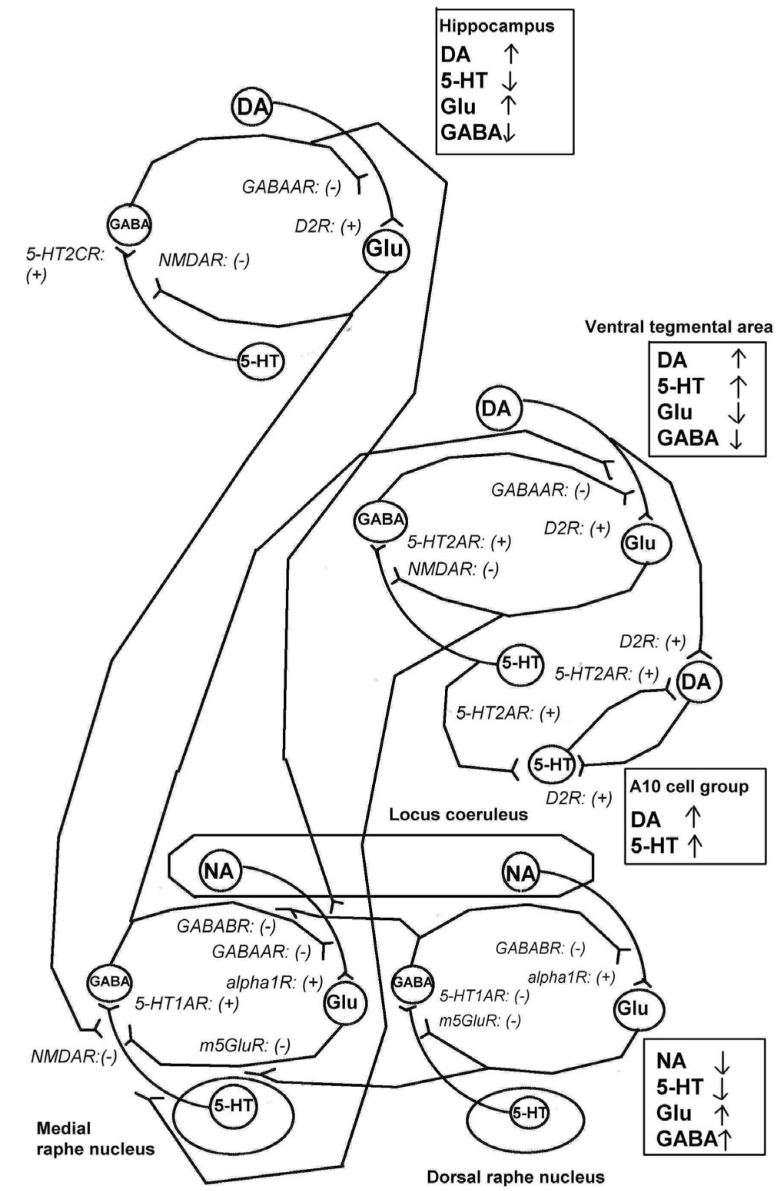

Figure 1: Neuronal pathways in the brainstem, ventral tegmental area and hippocampus in schizoaffective disorder. DA: dopamine, GABA: gamma-aminobutyric acid; Glu: glutamate; 5-HT: serotonin; NA: noradrenaline. Alpha1R: alpha1 receptor, a subtype of the noradrenergic receptor; D2R: D_2 receptor, a subtype of the dopaminergic receptor; GABAAR: $GABA_A$ receptor, a subtype of the GABAergic receptor, GABABR: $GABA_B$ receptor, a subtype of the GABAergic receptor; 5-HT1AR: $5\text{-}HT_{1A}$ receptor, a subtype of the serotonergic receptor; 5-HT2AR: $5\text{-}HT_{2A}$ receptor, a subtype of the serotonergic receptor; m5GluR: m5Glu receptor, a subtype of the metabotropic glutamatergic receptor; NMDAR: NMDA receptor, a subtype of the ionotropic glutamatergic receptor. A plus mark indicates a postsynaptic excitatory impulse; a minus mark indicates a presynaptic inhibitory impulse. ↑: increase; ↓: decrease.

receptors. The latter neurons activate GABAergic neurons, which inhibit alpha1 noradrenergic neurons via $GABA_B$ receptors. This neural circuit could be named "mood center". As consequence of the reciprocal influence of the described neurotransmitters upon each other, an increased presynaptic glutamatergic inhibition of $5\text{-}HT_{1A}$ serotonergic neurons, via m5Glu receptors, enhances serotonin hypoactivity and hyperactivity of presynaptic GABAergic neurons, via $GABA_B$ receptors, enhances noradrenaline hypoactivity. These neurotransmitter alterations could be associated with depressive symptoms. GABAergic neurons of the "mood center" inhibit other GABAergic neurons of the center for the circadian rhythm, via $GABA_B$ receptors, and glutamatergic neurons from the "mood center" inhibit other glutamatergic neurons of the center for the circadian rhythm, via m5Glu receptors [12]. In the hippocampus, D_2 dopaminergic neurons activate glutamatergic neurons which presynaptically inhibit $5\text{-}HT_{2C}$ neurons, via NMDA receptors. The latter neurons activate GABAergic neurons which presynaptically inhibit, via $GABA_A$ receptors, D_2 dopaminergic neurons. Glutamatergic neurons from the hippocampus inhibit $5\text{-}HT_{1A}$ serotonergic neurons in the brainstem, and GABAergic neurons from the hippocampus inhibit alpha1 noradrenergic neurons in the brainstem [4].

In the ventral tegmental area, in schizophrenia and schizoaffective disorder, D_2 dopaminergic neurons with an increased activity, due to the COMT or monoamine oxidase genes, activate glutamatergic neurons, which, due to the dysbindin-1 and neuregulin-1 genes, weakly inhibit via NMDA receptors 5-HT_{2A} serotonergic neurons. 5-HT_{2A} serotonergic neurons with hyperactivity, due to the serotonin transporter genes and the decreased presynaptic glutamatergic inhibition, activate GABAergic neurons, which via $GABA_A$ receptors weakly inhibit, as a consequence of the GAD 67 gene, D_2 dopaminergic neurons. In the A10 cell group, D_2 dopaminergic and 5-HT_{2A} serotonergic neurons, which are activated by dopaminergic and serotonergic neurons from the ventral tegmental area, activate each other and enhance dopamine and serotonin hyperactivity (Werner and Coveñas). GABAergic neurons from the center for the circadian rhythm in the brainstem inhibit D_2 dopaminergic neurons in the ventral tegmental area, and glutamatergic neurons from the ventral tegmental area inhibit, via NMDA receptors, 5-HT_{1A} serotonergic neurons in the center in the brainstem.

Treatment by second-generation antipsychotic drugs

Schizoaffective disorder is treated generally by second-generation antipsychotic drugs (SGAs) alone or in combination with mood-stabilizing drugs [12]. Among the SGAs, risperidone, olanzapine, quetiapine or clozapine are prescribed in most cases. Among the mood-stabilizing drugs, lithium, carbamazepine or lamotrigine are chosen.

Risperidone

Risperidone is a SGA with a D_2 and 5-HT_{2A} antagonistic effect and with a higher affinity for the D_2 receptor than olanzapine and quetiapine. Risperidone improves positive schizophrenic symptoms like haloperidol and improves negative schizophrenic symptoms to a lesser extent than olanzapine and quetiapine [23,24]. Besides, it improves manic symptoms. Because risperidone has a high affinity for the D_2 receptor, it often causes extrapyramidal symptoms (EPS).

Olanzapine

Olanzapine is a SGA with a D_2 and 5-HT_{2A} antagonistic effect and with a higher affinity for the 5-HT_{2A} receptor than risperidone. It improves positive and negative schizophrenic symptoms better than risperidone and causes EPS to a weaker extent than risperidone. Olanzapine is a safe SGA in the treatment of schizophrenic and manic symptoms [25].

Quetiapine

Quetiapine is a SGA with a D_2 and 5-HT_{2A} antagonistic effect and with a higher affinity for the 5-HT_{2A} receptor than olanazapine. It improves positive and negative schizophrenic symptoms like olanzapine and can be also used to treat depressive symptoms. It causes EPS to a lesser extent [8,23].

Clozapine

Clozapine is a SGA with a D_3, D_4 and 5-HT_{2A} antagonistic effect and improves positive and negative schizophrenic symptoms better than other antipsychotic drugs. It seldom causes EPS and can induce neutropenia in 3% and agranulocytosis in 0.8% of patients [26].

Treatment by mood stabilizers

In some schizoaffective patients, SGAs are combined with mood-stabilizing drugs, especially when affective symptoms alternate between depressive and manic symptoms. Among the mood-stabilizing drugs, we mention the mechanism of action and the therapeutic effect of lithium, carbamazepine and lamotrigine [12].

Lithium

Lithium is a mood-stabilizing drug with a therapeutic effect on affective symptoms. One third of the patients treated with lithium have no recurrence of affective symptoms. It decreases the excitatory effect of dopamine and glutamate and increases the presynaptic inhibitory effect of GABA. The main adverse effects are cardio- and nephro-toxicity [27].

Carbamazepine

Carbamazepine is an antiepileptic drug and a mood-stabilizing drug. It blocks fast-inactivated sodium channels. A combination of SGAs with carbamazepine has comparable therapeutic effect in schizoaffective patients like the administration of SGAs alone [28].

Lamotrigine

Lamotrigine is an antiepileptic drug and a mood-stabilizing drug. It blocks voltage-gated sodium channels and alpha4beta2 nicotinic cholinergic receptors and stabilizes dopaminergic neurons. In meta-analyses, it has been shown than lamotrigine combined with clozapine can treat successfully clozapine-resistant forms of schizophrenia and schizoaffective disorder [29].

Conclusion

Schizoaffective disorder, a chronic psychiatric disease, with schizophrenic and affective symptoms has a prevalance of 0.5% in the population. Susceptibility genes which encode dopamine hyperactivity and GABA and glutamate dysfunction have been discovered. In one third of the patients, traumata enhance alterations of classical neurotransmitters. Neurotransmitter alterations in schizophrenic and depressive symptoms have been described, while dopamine, noradrenaline and serotonin are postsynaptic excitatory neurotransmitters and GABA and glutamate presynaptic inhibitory neurotransmitters. Neural networks are described in the brainstem, hippocampus and ventral tegmental area, in which the coherence between the function of the susceptibility genes and the cellular mechanism is considered. The current pharmacotherapy of schizoaffective patients consists in administering second-generation antipsychotic drugs, for example risperidone, olanzapine, quetiapine or clozapine alone or in combination with mood-stabilizing drugs. Among the latter drugs, lithium can prevent recurrence of affective symptoms in one third of patients. In order to improve patients' adherence to the pharmacotherapy, it is important to combine this therapy with social integration and psychoeducation.

References

1. Klosterkötter J (2008) Indicated prevention of schizophrenia. Dtsch Arztebl Int 105: 532-539.
2. Huber G, Gross G (1989) The concept of basic symptoms in schizophrenic and schizoaffective psychoses. Recent Prog Med 80: 464-452.
3. Werner FM, Covenas R (2013) Classical neurotransmitters and neuropeptides involved in schizophrenia: How to choose the appropriate antipsychotic drug? Curr Drug Ther 8: 132-143.
4. Werner F-M, Covenas R (2012) Treatment of the schizoaffective disorder according to a neuronal network. Klin Neurophysiol 43: 103-104.
5. Werner F-M, Covenas R (2010) Classical neurotransmitters and neuropeptides involved in major depression: a review. Int J Neurosci 120: 455-470.
6. Werner F-M, Covenas R (2013) Classical neurotransmitters and neuropeptides involved in major depression: a focus on antidepressant drugs. Curr Med Chem 20: 4853-1858.
7. Haller SC, Padmanabhan JL, Lizano P, Torous J, Keshavan M (2014) Recent advances in understanding schizophrenia. F1000 Prime Reports 6: 57.

8. Werner F-M, Covenas R (2014) Safety of antipsychotic drugs: focus on therapeutic and adverse effects. Exp Opin Drug Saf 13: 1031-1042.

9. Rajina P (2008) Antiepileptic drugs as mood stabilizers: what did we learn from the epileptology? Ideggyogy Sz 61: 305-316.

10. Werner FM (2006) Schizophrenia: from the genetic localization to the cellular mechanism. Klin Neuro 37: 19-20.

11. Collier DA, Li T (2003) The genetics of schizophrenia: glutamate not dopamine? Eur J Pharmacol; 480: 177-184.

12. Werner F-M, Covenas R (2016) Classical Neurotransmitters and NeuropeptidesInvolved in Schizoaffective Disorder: Focus On Prophylactic Medication. BenthamSciencePublishers Sharjah.

13. Andersson RH, Johnston A, Herman PA, Winzer-Serhan UH, Karavanova I, et al. (2012) Neuregulin and dopamine modulation of hippocampal gamma oscillations is dependent on dopamine D4 receptors. Proc Natl Acad Sci USA 2012; 109: 13118-13123.

14. Nilsson M, Waters S, Waters N, Carlsson A, Carlsson ML (2001) A behavioural pattern analysis of hypoglutaminergic mice-effects of four different antipsychotic agents. J Neural Transm 108: 1181-1196.

15. Liu Y, Tang Y, Pu W, Zhang X, Zhao J (2011) Concentration of DA, Glu and GABA in brain tissues in schizophrenia developmental model rats induced by MK-801. Zhong Nan Da Xue Xue Bao Yi Ban 36: 712-719.

16. Glausier JR, Kimoto S, Fish KN, Lewis DA (2015) Lower Glutamic Acid Decarboxylase 65-kDa Isoform Messenger RNA and Protein Levels in the Prefrontal Cortex in Schizoaffective Disorder but Not in Schizophrenia. Bio Psychiatry 77: 167-176.

17. Modhaddam B, Javitt D (2011) From revolution to evolution: the glutamate hypothesis of schizophrenia and its implication for treatment. Neuropsychopharmacology 37: 4-15.

18. Nutt DJ, Demyttenaere K, Janka K, Aarre T, Bourin M, et al. (2007) The other face of depression, reduced positive effect: the role of catecholamines in causation and cure. J Psychopharmacol; 21: 461-471.

19. Hieronymus F, Emisson JF, Nilsson S, Eriksson E. (2015) Consistent superiority of selective serotonin reuptake inhibitors over placebo in reducing depressed mood in patients with major depression.

20. Sennfelt DA, Marques da Silva MA, Tavares AP (2011) Bupropion in the treatment of major depressive disorder in real-life practice. Clin Drug Investig; 31: 19-24.

21. Nowak G, Partyka A, Palucha A, Szawczyk B, Wieronska JM, et al. (2006) Antidepressant-like activity of CGP 36742 and CGP 51176, selective GABAB receptor antagonists, in rodents. Br J Pharmacol; 159: 581-590.

22. Iodarola ND, Niciu MJ, Richards EM, Vande Voort JL, Ballard ED, et al. (2015) Ketamine or other N-methyl-D-aspartate receptor antagonists in the treatment of depression: a perspective review. Ther Adv Chronic Dis 6: 97-114.

23. Werner FM, Coveñas R. (2014) Classical Neurotransmitters and Neuropeptides Involved In Schizophrenia: How to improve the Therapeutic Effect of the Antipsychotic Drugs. J Pharm Pharmacol 2: 571-581.

24. Venkatesh PR, Kozielska M, Suleiman AA, et al. (2013) Pharmacokinetic-pharmacodynamic modeling of antipsychotic drugs in patients with schizophrenia Part II: The use of subscales of the PANSS score. Schizophr Res 146: 153-161.

25. Huang CL, Hwang TJ, Chen YH, Huang GH, Hsieh MH, et al.(2015) Intramuscular olanzapine versus intramuscular haloperidol plus lorazepam for the treatment of acute schizophrenia with agitation: An open-label, randomized, controlled trial. J Formos Med Assoc 114: 438-445.

26. Shang DW, Li LJ, Wang XP (2013) Population pharmacokinetic/ pharmacodynamic model for clozapine for characterising the relationship between accumulated exposure and PANSS scores in patients with schizophrenia. Ther Drug Monit published online 13 December.

27. Malhi GS, Tanious M, Coulston CM, Berk M (2013) Potential mechanisms of action of lithium in bipolar disorder: current understanding. CNS Drugs 27: 135-153.

28. Kulkarni J, Filia S, Berk L, Filia K, Dodd S, et al. (2012) Treatment and outcomes of an Australian cohort of outpatients with bipolar I or schizoaffective disorder over twenty-four months: implications for clinical practice. BMC Psychiatry 12: 228.

29. Tiihonen J, Wahlbeck K, Kivienemi V (2009) The efficacy of lamotrigine in clozapine-resistant schizophrenia: a systematic review and meta-analysis. Schizophr Res 109: 10-14.