Column: New in Psychopharmacology

A SELECTIVE SUMMARY OF PSYCHOPHARMACOLOGY RESEARCH PUBLISHED IN 2016

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Psychopharmacology circles have been expressing growing concerns about the stagnation in the marketing of new medications despite a better understanding of pathophysiology and recognition of new potential targets. The U.S. Food and Drug Administration (FDA) approved two psychotropic medications — cariprazine and brexpiprazole in 2015. As at November 2016, Primavanserin (a medication for psychosis in parkinsonism) is the only new drug to enter the market. There is greater interest in looking deeply at older, well-established treatments and learning from existing psychoactive substances. An increasing focus on safety and side effects burden is necessitating prescribers to review risk benefit analysis. A collection of articles published in 2016 are summarised below. The articles are selected for being interesting, inspiring or of immediate relevance to clinical practice.

DOES LITHIUM INCREASE CANCER RISK?

Lithium is the most established primary mood stabilizer for maintenance treatment of bipolar disorder. Negative effects on renal functioning prevent clinicians from prescribing lithium to many who might benefit from this medication. Reports of higher risk of renal tumours among lithium users, though inconsistent, have added to this reluctance.[1] Martinsson et al investigated this issue using the nationwide Swedish inpatient medical registries.[2] The prescription registry provided information on exposure and regularity of purchase. Incidence rate of first cancer and site specific cancer diagnosis between 2005 and 2009 for patients between 50 and 84 years of age were calculated. Among 2593011 general population subjects in the database, there were 2393 subjects with bipolar disorder and on lithium treatment. 3049 bipolar disorder patients were not on lithium treatment. In patients with bipolar disorder, six percentage had cancer compared with 6.4% in general population. Five percentage of bipolar patients on lithium had cancer compared to six percentage in those not on lithium treatment. Overall risk of cancer was not different among the groups. The study concluded that lithium treatment is not associated with an increase in the risk of cancer. Patients with bipolar disorder and not on lithium showed an increased risk of cancers in GI, respiratory and intrathoracic organs. Low numbers of cancer cases among risk subgroups and lack of controlling for confounding factors are the main limitations of this study.

An interesting discussion around this issue is whether the neuroprotective effect of lithium, explained by its potential ability to increase telomere length, has something to do with risk of cancer. Longer telomere length is associated with various cancers. Lithium's ability to activate telomerase may theoretically increase the risk of cancers.[3] Effect of lithium on GSK-3Beta is also suggested as another route to either protection or promotion of cancer.[4] It is unclear how these different mechanisms counterbalance and translate to cellular changes.

Please cite this article as: Kumar MT. A selective summary of psychopharmacology research published in 2016. Kerala Journal of Psychiatry 2016; 29(1):63-75.

A study using the national health database of Taiwan investigated the lithium and cancer risk association among patients who have received a bipolar disorder diagnosis between 1998 and 2009.[5] They compared cancer incidences between lithium group and anticonvulsant group. The study identified 4729 individuals with bipolar disorder of which 7.8% were on lithium compared with 67% on anticonvulsants; 24% were on both medications. The study identified 115 cancer cases with 29 among lithium group and 86 among anticonvulsant only group. This study concluded that lithium exposure is associated with significantly lower cancer risk (as compared to anticonvulsants) with further risk reduction accruing from increasing cumulative doses of lithium. The study showed an overall 27% decrease in risk in the lithium group when compared to those on anticonvulsants. Two other large population based studies from Denmark, published this year, have also shown that lithium does not increase risk of renal or upper urinary tract cancers.[6,7]

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CAN LITHIUM OFFER NEUROPROTECTION?

Lithium can inhibit neuronal apoptosis and enhance neuronal growth,[1,2] and animal studies have repeatedly confirmed it. With such an effect, it is likely that patients taking lithium for long periods may have less neurological disorders. Prosser et al. reviewed charts of adult patients on lithium in four specialist lithium clinics in New York.[3] Of the 8000 patients registered in these clinics, 1028 randomly selected cases were analyzed to see whether lithium intake is associated with excess cardiovascular and neurological disorders. Fifty-six percentage of this group received regular lithium. Psychiatric disorders were re-categorized as bipolar, unipolar and others. 10.7% of the participants received neuro or cardiac disorder diagnosis. Patients who received lithium recorded a reduced chance of having neuro or cardiac disorders. Logistic regression showed that lithium treatment was associated with reduced risk of some these conditions. Age and treatment with antipsychotics were associated with an increase in the risk.

This chart review did not control for confounding factors. Many of the subgroups of neuro and cardiac conditions recorded a very small number of cases. Therefore, the conclusions are less robust. The results of this study support previous observations of reduced risk of dementia among bipolar patients taking lithium. A large observational study of Danish patients between 1995 and 2005 found that although patients with a diagnosis of bipolar disorder have an increased risk of developing dementia, the rates of dementia in patients who use lithium regularly is similar to the rates in the general population.[4] Some other studies have shown that lithium reduces the risk of dementia in bipolar patients to the same level as in the general population.[5]

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ARE SSRIS SAFE IN PREGNANCY?

Antenatal depression is associated with maternal health risks and long term emotional behavioral, and social problems in the children.[1,2] Pregnant women with depression are often prescribed SSRIs and SNRIs. Effect of such exposure during early developmental period is not well understood. A large population based study from Canada has reported high risk of autistic spectrum disorders among children who were exposed to SSRI during second or third trimester of pregnancy.[3] Transient neonatal adaptation symptoms are reported to be five times more common among SSRI exposed newborns.[4] What is the effect of such exposure beyond the withdrawal symptom stage?

In a prospective naturalistic study, Salisbury et al. studied pregnant women between ages 18-40 who were taking SSRIs for unipolar mood disorder.[5] Infants were studied for one month post-partum. Exposure was defined as taking SSRIs for at least four weeks at any time during pregnancy. During the first month of life, infant neurobehavioral characteristics like attention, arousal, excitability, lethargy, habituation, self-regulation and quality of movements were comprehensively studied at several time points by observation of neurological and behavioral function through elicited responses, reflexes, and social interaction with the infant. Eighty-one percentage of participants in this study took SSRI through the delivery. Sixty-one percentage took sertraline and 16% were on citalopram. Infants in both SSRI and SSRI plus benzodiazepines exposure groups had lower quality of movements than those in non-exposed group. The infants in the exposure groups also had more CNS stress signs. Neurobehavioral symptoms were seen beyond the first week, therefore ruling out the possibility of the observed changes being withdrawal symptoms. SSRI-exposed children had poorer self-regulation. Infants with concomitant benzodiazepine exposure had the lowest movement quality scores and highest number of CNS stress signs. It is interesting to note that there were no differences seen between infants whose mothers reported discontinuation of the SSRI prior to the last month of pregnancy and infants whose mothers continued SSRI use through delivery. This show that third-trimester discontinuation of SSRI medication did not prevent neonatal adaptation signs. Thus, the findings do not support discontinuing SSRI medications in the third trimester. Infants in the SSRI plus benzodiazepine group had the least favorable scores, alerting clinicians to avoid benzodiazepines as far as possible. This is the first study to show that neuro-behavioral effects of SSRIs persist beyond the withdrawal period and that this effect is more pronounced in those who receive polytherapy. The observed risks have to be balanced with the risk of ongoing depression and its impact on the fetus and the infant.

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ARE ANTIDEPRESSANTS USELESS IN CHILDREN?

Major depression affects 3% of children aged 6- 12 years and 6% of those aged 13 to 18 years.[1] Most guidelines suggest psychological treatments as the first line of management.[2] There are safety warnings against the use of antidepressants in children. Cipriani and colleagues conducted a network meta-analysis of all randomized double blind trials published up to 2015, comparing the effects of 14 antidepressants in children and adolescents.[3] They included 34 trials with 5260 participants. Only fluoxetine was significantly more effective than placebo with a medium effect size (SMD –0·51, 95% CI –0·99 to –0·03). The confidence interval was large and close to the point of no difference, raising questions as to usefulness in clinical practice. When tolerability is also taken into account, benefits outweighed the risks only for fluoxetine. Venlafaxine, duloxetine and imipramine had the worst tolerability profiles. Venlafaxine was associated with increased suicidal thoughts and attempts. There were not enough studies to comment on other medications. This meta-analysis shows that fluoxetine might reduce symptoms in children and adolescents with depression and this might be the only medication of choice in this age group. It has to be noted, however, that the overall quality of evidence was rated as low.

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HOW EFFECTIVE IS VORTIOXETINE IN DEPRESSION?

Less than 50% of patients achieve full remission from depressive episode with first line therapy. One third do not achieve remission even after therapy with as many as four antidepressants and this is the driver behind the search for newer antidepressants.[1] Vortioxetine is a multi-modal antidepressant (inhibitor of serotonin transporter as well as antagonism at receptors) that was approved by U.S. FDA in 2013. Thase et al. conducted an aggregate data meta-analysis of all randomized placebo controlled trials of vortioxetine in the approved dosage range of 5 to 20 mg/day.[2]

Eleven short term placebo controlled trials were included in the analysis. When compared to placebo, patients treated with 10 mg/day reported a mean difference in change from baseline in the depression total score (MADRS) of 3.57 points. A reduction of at least two points is usually considered clinically meaningful. The medication was associated with greater reduction in MADRS total score compared to placebo in patients receiving five mg (n=840, Δ 2.27 points, p=0.007), 10 mg (n=877, Δ 3.57 points, p <0.001), and 20 mg (n=671, Δ 4.57 points, p <0.001). 15 mg was not statistically superior to placebo. Remission rates were 23.8% (placebo) vs 30.2%(10 mg), 28.7% (15 mg), and 32.2% (20mg). Response rates were 36.7% (placebo), 48.8%, (10 mg), 46.3% (15 mg), and

51.6% (20 mg). The analysis shows that 5 mg, 10 mg and 20 mg vortioxetine are more effective than placebo in the treatment of depression. 15 mg dose failed to differentiate from placebo on all measures. Authors opine that this is due to small sample size in the 15mg dose group. The findings are generally similar to the previous meta-analyses.

Another meta-analysis investigated the efficacy of vortioxetine in depression with significant anxiety.[3] Such patients have greater functional disability and higher risk of suicidal ideas. High level of anxiety in depression is considered as a poor response indicator. Vortioxetine's multimodal action is expected to make it more suitable for this group. The review included efficacy data from 10 studies with 1590 major depression patients treated with placebo and 2856 treated with therapeutic dosages of vortioxetine. Nearly half of all patients in both groups had a baseline anxiety total score (HAM-A) greater than 20. Total depression score (MADRS) change in patients with high anxiety was significantly in favor of vortioxetine (5, 10, and 20mg). Here too, the 15 mg dosage did not show any difference with placebo. In the subgroup with very high anxiety, only doses of 5 and 10 mg were superior to placebo. Authors consider insufficient sample sizes as the reason for lack of effect at higher doses.

A third meta-analysis was reported by Li et al.[4] This included trials of 10 mg vortioxetine. Six RCTs with 1801 patients were included in this analysis. They found patients on the 10 mg dosage to have higher response rate than those treated with placebo (RR =1.50; 95% CI: 1.32, 1.70; *P*,0.001). Vortioxetine 10 mg also significantly reduced the total depression (MADRS) score (WMD =-3.27; 95% CI: -4.88, -1.66; *P*,0.001). Vortioxetine was associated with higher incidence of nausea (RR =3.44; 95% CI: 2.63, 4.48; *P*,0.001), vomiting (RR =2.78; 95% CI: 1.32, 5.85; *P*=0.007), constipation (RR =2.03; 95% CI: 1.15, 3.58; *P*=0.015), and hyperhidrosis (RR =4.44; 95% CI: 1.29, 15.26; *P*=0.018).

In summary, recent meta-analyses show that 5mg, 10mg and 20 mg doses of vortioxetine are superior to placebo. In the absence of head to head trials, it is difficult to estimate how superior this is to existing antidepressants.

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OMEGA 3 IN DEPRESSION… FINAL ANSWERS?

Effect of Omega 3 fatty acids on depression is not yet established beyond doubt. This may be due to differences in formulations tested. It is likely that only Eicosa Pentaenoic Acid (EPA) predominant formulations, as opposed to Decosahexaenoic acid (DHA) predominant ones, have antidepressant effects.[1] EPA has anti-inflammatory properties which may be important for its antidepressant effect. Previous studies have included patients with milder depression. This led to a larger placebo response and regression to mean, thus reducing the effect of the active agent under study. Hallahan et al. evaluated whether EPA-predominant formulations have greater efficacy, when compared with DHA-predominant formulations, for depressive symptoms.[2] They also tested whether a diagnosis of depression is required for these to be effective.

They included all double-blind, placebo-controlled studies of adults and children that examined the antidepressant effect of omega-3 HUFAs either as a

monotherapy or when augmented with psychotropic agents

43 RCTs were included in the analysis. EPA-predominant formulations demonstrated a superior antidepressant efficacy compared with placebo (G = 0.34, 95% CI .21–0.47, P<.001). DHA-predominant preparations consistently demonstrated no benefit over placebo (G = 0.03, 95% CI –0.12 to 0.19, P < 0.66). Among populations with a diagnosed depressive episode, EPA-predominant formulations demonstrated a significant benefit compared with placebo (G=0.61, 95% CI 0.38–0.85, P < 0.001). No benefit was demonstrated for the populations without a formal diagnosis of depression (G = 0.08, 95% CI 70.01 to 0.17, P< 0.07). EPA was effective in both augmentation (G = 0.59, 95% CI 0.42–0.77, P = 0.004, I^2 = 57%) and monotherapy (G = 0.33, 95% CI 0.13–0.52, P50.003, I 2 = 68%).

This analysis concludes that EPA-predominant formulations are more efficacious than placebo for treatment of clinical depression. DHA-predominant formulations are consistently and homogenously ineffective.

Humans are unable to synthesize EPA or DHA de novo and only make limited amounts of DHA and EPA from the dietary precursor alpha-linolenic acid. It is suggested that supplemented EPA is rapidly incorporated into membrane phospholipids of circulating mononuclear cells. This reduces the production of proinflammatory cytokines. The resulting anti-inflammatory effect may be linked to the observed antidepressant effects. This analysis suggests that EPA rich formulations are beneficial in clinical depression. Larger trials that include monitoring of treatment adherence and biochemical levels would be required to establish this beyond doubt.

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CAN LURASIDONE HELP IN DEPRESSION WITH MIXED FEATURES?

Mixed features variant is a severe form of major depression characterized by hypomanic symptoms below the threshold for hypomania in patients with no history of mania or hypomania. This is characterized by greater illness severity, suicidal behavior and poorer outcomes. There are no controlled studies that have examined the effect of any psychotropic agents in this group of patients. Atypical antipsychotics and mood stabilizers are usually suggested as treatment options.[1,2] Suppes et al. investigated the efficacy of lurasidone in this condition.[3] Adult outpatients with depression and having a MADRS score of 26 or above were recruited. These patients had hypomanic/manic symptoms for most days in the two weeks prior to screening. Participants received 6 weeks of lurasidone or placebo. The primary efficacy endpoint was mean change in MADRS total score from baseline to week 6. 208 patients received at least one dose of study medication. Daily dose of lurasidone was 20 mg for 32% of patients, 40 mg for 29%, and 60 mg for 39%. Primary endpoint was significantly greater for lurasidone compared with placebo (220.5 and 213.0, respectively; p,0.001; effect size, 0.80)

64.8% of patients on lurasidone met response criteria compared with 30.0% (p <0.001, NNT =3) in placebo group. 49% of lurasidone group remitted while only 23% in placebo group achieved this. Nausea, somnolence, dizziness, akathisia, dry mouth, and parkinsonism were reported more in the lurasidone group. Interestingly, more patients in placebo group discontinued due to side effects (5% vs 2.8%).

This is the first placebo-controlled clinical trial that included patients with major depressive disorder associated with subthreshold hypomanic symptoms.

Previously, lurasidone has shown efficacy in bipolar depression in the dose range 20-120mg/day. This study shows that lower dose of lurasidone is effective in mixed features.

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CAN CARIPRAZINE BRING HOPE IN BIPOLAR DEPRESSION?

Quetiapine and lurasidone are the only FDA approved antipsychotic medications for bipolar depression. Treatment options remain limited in bipolar depression. Cariprazine is a dopamine receptor partial agonist with particular affinity to D3. D3 receptors are thought to be important in motivation and reward. Therefore, cariprazine may be effective in improving anhedonia.

Suresh Durgam and colleagues report the results of an 8 week randomized double blind placebo controlled parallel group study in adults with bipolar depression.[1] Cariprazine was initiated at 0.5 mg/day and increased to 1.5 mg on day three. Further increases were made in higher dose parallel groups on days 5 and 8. In the 3 mg group, this dose was achieved on day 15. MADRS, CGI and HAMD were the outcome measures. 584 patients were randomly assigned and 73% of them completed the study.

MADRS score change from baseline to week 6 was statistically significant in favor of cariprazine at 1.5 mg/day compared with placebo (adjusted p=0.003). Doses of 0.75 mg and 3 mg did not make a statistically significant difference. Higher doses reported more akathisia and insomnia. Akathisia, anxiety and agitation led to most of the discontinuations. Excluding this, the incidence of extrapyramidal symptom-related adverse events was low across groups. Somnolence, sedation, and weight gain were generally low and descriptively similar for placebo and cariprazine. Higher fasting glucose and triglyceride levels were seen with cariprazine at 3.0 mg/day but this was not the case at 1.5 mg/day.

The study is limited by short treatment duration and lack of an active comparator. 1.5 mg/day demonstrated efficacy and safety, suggesting that it may be an effective dosage for the treatment of bipolar I depression.

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ARE ANTIDEPRESSANTS INEFFECTIVE IN OLD AGE?

10-15% of elderly suffer from depression.[1] Depression is associated with poor quality of life and high mortality. Previous metaanalyses have shown the benefit of antidepressants in this age group.[2] Swedish researchers led by Tham conducted an updated metaanalysis with a comprehensive search which identified 12 RCTs. Most of these studies evaluated acute management of depression for eight weeks.

When SSRI was compared to placebo in acute treatment (366 receiving placebo and 517 treated with an SSRI), there was no significant difference between groups for response (OR: 0.86, 95% CI: 0.51–1.10) or remission (OR: 0.79, 95% CI: 0.61–1.03) after eight weeks of treatment. The proportion achieving a positive response was 41% for SSRI versus 43% for the placebo. The proportion achieving remission was 32% for SSRI and 35% for the placebo.

The meta-analysis of duloxetine trials (247 on placebo treatment and 352 on duloxetine) showed that significantly more patients respond to acute treatment with duloxetine than to a placebo (OR: 2.83, 95% CI: 1.96–4.08). The quality of evidence was rated as low for these studies. Significantly more patients achieved remission with duloxetine (32% vs 21%) (OR: 1.78, 95% CI: 1.20–2.65). Agomelatine and bupropion were found to be better than the placebo for response (60% vs. 34% and 53% vs. 43% respectively), but not with respect to remission.

This analysis shows that in people 65 years of age and older, SSRIs as a group may not offer any benefits over placebo in acute treatment trials of up to eight weeks duration. The serotonin norepinephrine reuptake inhibitor duloxetine is superior to placebo in achieving remission and response in this group. It is important to note that there was no RCT on mirtazapine in this patient group, though many psychiatrists often prefer to use mirtazapine for acute depression in elderly.

Previous metaanalyses[2,3] have found overall superior effect for antidepressants in old age. Differences in study population (for e.g.: duloxetine trials recruited only patients with recurrent depressive disorder) and age groups (less effect in 65 plus in general as well as greater effect in severely depressed 75 plus age group) may explain some of the disparities in conclusions. Prescribing is a hard task when evidence is inconsistent, especially across metaanalyses.

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DANGEROUS SIDE EFFECTS OF QUINOLONES

Quinolones are broad spectrum antibiotics that are widely used. They inhibit key enzymes involved in bacterial DNA replication. Many quinolones have been withdrawn from market due to serious side effects. This include temafloxacin for hemolytic anemia, trovafloxacin for hepatotoxicity, grepafloxacin for QTc interval prolongation, clinafloxacin for phototoxicity, and gatifloxacin for dysglycemia. There are restrictions regarding the use of other quinolones (including norfloxacin) in some countries. Some quinolones are associated with psychiatric adverse reactions including violent suicidal behaviors. Ofloxacin, levofloxacin, and ciprofloxacin have been associated with violent suicide in relatively short time after exposure. European Medicine Agency recently confirmed the emergence of such warning signals from several sources. Samyde and colleagues analyzed the WHO adverse drug reactions database (Vigibase) to estimate the prevalence of this dangerous side effect.1 Vigibase is the largest and most comprehensive international drug monitoring database covering 110 countries. Every year, one million individual case safety reports are added to this. Authors extracted reports of adverse reaction associated with antibiotic use recorded between 1970 and 2015. They identified 992097 adverse events associated with antibiotic use. Reported cases of suicidal behavior were 1627 (0.2%). Among the adverse events with exposure to quinolones, there were 608 cases of suicidal behavior including 97 cases of completed suicide.

Ciprofloxacin was the most frequently used quinolone in the reports of suicidal behavior (43.2% of the cases), followed by levofloxacin (26.6%), moxifloxacin (14.9%) and ofloxacin (11.4%). In total, 13.7% of the quinolone-related cases of suicidal behavior were also exposed to antidepressants and 5.8% to antipsychotics.

Overall, the use of quinolones was associated with a significantly increased reporting of suicidal behavior compared with other antibiotics (adjusted OR 2.78, 95% CI: 2.51–3.08). Ciprofloxacin showed strongest association with suicidal behaviors (adjusted OR 4.01, 95% CI 3.50–4.59). Ofloxacin showed the strongest association with reporting of depressive disorders (adjusted ROR 5.99, 95% CI 5.20–6.89).

GABA antagonistic effects of quinolones can lead to increase in anxiety.2 Repeated administration of ciprofloxacin in rats is shown to reduce brain serotonin and induce anxiety. It is also thought that quinolones may activate NMDA receptors which could be relevant to suicidal behaviors.

The results of this study serve as a reminder for all of us to be comprehensive in collecting recent treatment history while assessing patients with recent onset suicidal ideas and acts. Psychiatrists need to warn medical colleagues on this potential risk, especially in places where antibiotic overuse is common.

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NEW RECOMMENDATIONS FOR MANAGING ANTIPSYCHOTIC INDUCED WEIGHT GAIN

British Association of Psychopharmacology (BAP) comprehensively reviewed evidence for various interventions in managing antipsychotic side effects, to produce a new management guideline.[1] Weight management recommendations are particularly important, as they are likely to change clinical practice significantly. Life style interventions are the first recommendation as they have generally shown consistent positive effect. These are likely to reduce BMI by approximately by 1 kg/m^2 or more when compared to the control treatment. An increase of 1 kg/m^2 in BMI results in 8.4% increase in risk for the development of diabetes. Switching to relatively weight neutral medications like haloperidol, ziprasidone, lurasidone, aripiprazole, amisulpride and asenapine is the second strategy supported by good quality evidence. Adjunctive aripiprazole is recommended as a possible intervention for weight gain associated with clozapine and olanzapine. It is unknown whether this adjunctive treatment would work with other antipsychotics. Once the above recommendations are exhausted, BAP suggests that clinicians consider prescribing adjunctive metformin. Short term trials have found that metformin reduces weight by approximately three kg as compared to placebo. In first episode initiations of antipsychotics, this effect might be even bigger — i.e., reduction by approximately five kg compared to placebo. Other medications that may reduce weight like orlistat and topiramate are limited by unacceptable side effects. Reboxetine's reported weight loss effect has not been independently replicated. Very limited data is available on beneficial effects reported for amantadine, melatonin and zonisamide. This guidance would definitely help clinicians to reduce the physical health burden secondary to antipsychotic use.

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DO ANTIDEPRESSANTS INCREASE CARDIAC RISK?

Antidepressant use has substantially increased in most of the countries during past many years. There is growing concern about the side effect burden of these medications. Since the FDA warning in 2011

regarding QTc prolongation, cardiac monitoring has become routine in many countries. However, studies have not clearly established a clear link between SSRI use and increased risk of arrhythmia. Carol Coupland and colleagues used the UK General Practice database to examine associations between different antidepressant drugs and the risk of myocardial infarction, arrhythmia, and stroke/transient ischemic attack[1]. This database has 12 million patient records. The study cohort included patients with a first computer recorded diagnosis of depression between the ages of 20 and 64 years. Patients with a previous recorded diagnosis of depression, other psychiatric diagnoses or any of the three outcome conditions were excluded. Those who were on antidepressants in the past were also excluded. New diagnosis of arrhythmia, myocardial infarction and stroke or transient ischemic attack were the outcomes for the analyses. Of the 2,38,963 patients who met the inclusion criteria, 87.7% received antidepressants during the study period. 71.3% of this were SSRIs. During the first five years of follow-up, 1452 new diagnoses of arrhythmia were made, giving an incidence rate of 16.2 per 10,000 person years.

Authors found no significant association with arrhythmia, over a five-year period, for any of the drug classes. A significant increase in the rate of arrhythmia was noted in the first 28 days after starting treatment with tricyclic and related antidepressants (adjusted hazard ratio 1.99, 1.27 to 3.13; P=0.003). There was also a significant reduction from 84 days after starting SSRIs (0.78, 0.66 to 0.92; P=0.004). No significant associations were found between antidepressant class and myocardial infarction during this period. In the first year of follow-up, patients treated with SSRI had a significantly reduced risk of myocardial infarction. No significant associations were found between antidepressant class or individual drugs and risk of stroke or transient ischemic attack.

Citalopram was not significantly associated with arrhythmia, even when given at doses of 40 mg or more. However, this finding is based on a small overall number of patients, and the warnings by regulatory agencies regarding high dose citalopram should remain valid clinically. This large observational study is reassuring about the cardiac safety of antidepressant medications.

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EVIDENCE FOR METOCLOPRAMIDE IN HYPERSALIVATION TREATMENT

Clozapine induced hypersalivation significantly reduces the quality of life of the patients and the existing treatment options offer only limited relief. Kreinin et al. studied the effect of metoclopramide in a three week placebo double blind RCT.[1] 58 patients with chronic psychotic illness and on stable dose of clozapine were randomized to receive 10 mg of metoclopramide or placebo for the first week, followed by 20 mg or 30 mg as needed. Nocturnal Hypersalivation Rating Scale (NHRS) and Drooling Severity Scale (DSS) were used to monitor the benefits. Metoclopramide at 30 mg was associated with a 54% reduction in NHRS compared to 20% on placebo. On DSS, this was 32% and 15% respectively. 67% of those on metoclopramide demonstrated disappearance or significant improvement compared with 29% on placebo. It is not known whether this effect would sustain with long term use. The effect of metoclopramide stratified by initial hypersalivation severity could have been useful, if provided. A longer trial with fixed dose medication and monitoring of twenty-four hours salivation and clozapine blood levels would be key to establish the benefit of this novel treatment.

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IS ADDING ANTIDEPRESSANTS TO ANTIPSYCHOTICS USEFUL?

One third of patients with schizophrenia have significant depressive and negative symptoms. Antidepressants are often added to antipsychotics to treat these symptoms.[1] Many guidelines hesitate to endorse this, as the efficacy and safety remain unclear. Helfer and colleagues conducted a meta-analysis in order to provide clarity on this important clinical problem.[2] All randomized trials published before 2015 and meeting broad inclusion criteria were included. The main analysis included 82 randomized controlled trials with a total of 3,608 participants. 92% of these studies were double blind. Median duration was 8 weeks. Add-on antidepressants appeared more efficacious than the control (add-on placebo or no adjunctive treatment) for both depressive symptoms (42 trials, 1,849 participants, SMD: –0.25, 95% CI=–0.38 to –0.12; NNT: 9, 95% CI=7 to 29 and negative symptoms (48 trials, 1,905 participants, SMD: –0.30, 95% CI=–0.44 to –0.16; NNT: 9, 95% CI=7 to 14).

Analysis also showed that adding antidepressants also improved overall symptoms and quality of life. Addition of antidepressants did not exacerbate psychosis or cause a rise in dropout rates. Abdominal pain, constipation, dizziness and dry mouth appeared more in the antidepressant group. Addition of antidepressants did not lead to an increase in abnormal movements.

For depressive symptoms, there were no subgroup differences in efficacy for individual antidepressants and drug classes. Post hoc analysis suggests that in patients with schizophrenia who are also clinically depressed, SSRIs are significantly more efficacious than the control. SSRIs and tetracyclic antidepressants were more effective in negative symptoms.

It has to be noted that the effect sizes for antidepressant addition were generally small, but were higher when only patients with pronounced depressive and predominant negative symptoms were included. Many of the reviewed studies were smaller in size and thus prone to smaller study effects like inflated effect sizes. As a class, only SSRIs appear to demonstrate a significant beneficial effect for negative symptoms (with citalopram and fluvoxamine showing consistent efficacy) and clinical depression in people with schizophrenia. Analysis shows that addition of antidepressants is generally safe.

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CAN ECT IMPROVE NEURO COGNITION?

ECT is a lifesaving treatment. Adverse effects on cognition remain the main reason for limited use of ECT.[1] Some previous studies have also shown that certain cognitive functions improve after ECT.[2] Lack of systematic monitoring has made interpretations of such studies difficult. Mohn and Rudd report the early results from an ongoing study about this.[3] Depressed subjects between ages 18 and 70 and undergoing ECT in south eastern Norway were recruited to this study. ECT dose and number of stimulations were customized for each patient. All patients received brief pulse (0.5 ms) stimulation two or three times a week. Mean number of stimulation per ECT series was 12. Right unilateral electrode placement was used in majority of cases. Anesthetic agents were alfentanil, propofol, or thiopental. Succinylcholine was used as muscle relaxant. The participants were cognitively assessed one to three days before the start of ECT using the MATRICS Consensus Cognitive Battery (MCCB) consisting of 10 tests assessing seven cognitive domains. These tests were repeated 6 weeks after completion of ECT. The depression score (MADRS) nearly halved post ECT treatment. Speed of Processing, Attention/Vigilance, and

Visual Learning significantly improved after ECT. There was no change in subjective memory scores. Subjective memory complaints appear to be related to depression severity rather than cognitive scores. The cognitive domains reported to have improved in this study are similar to the domains reported in previous studies.

Retrograde amnesia for personal events is the most consistently reported side effect of ECT. Assessment is time consuming and was not carried out in this study. Small sample size is a major limitation of this study. MCCB was originally developed for schizophrenia, though it has been increasingly used in depression research recently. This is an ongoing program and it would be interesting to see the long-term effects of ECT on cognition.

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ECT CAN IMPROVE BRAIN VOLUME

ECT is shown to improve neural plasticity in limbic regions. It can reverse the hyper connectivity between certain frontal and limbic regions as seen in depression.[1] Cerebellum, with its role in affective, cognitive and attentional processes, is another area thought to be relevant to depression and ECT. Ictal involvement of cerebellum is considered by some as an important element of ECT efficacy. Depping et al. studied changes in cerebellar volume in depressed patients treated with ECT.[2] Twelve patients with medication resistant depression were treated with right unilateral brief pulse ECT. This was given three times a week, with the number and dose of stimulations being determined by clinical needs. Drug regimens remained mostly unaltered during ECT. All control subjects were healthy and medication-free. MRI was done five days prior to ECT and 6 to 8 days after last ECT session. At baseline, depression was characterized by increased volume in specific cerebellar areas on both sides compared to controls. These remained unchanged with ECT but there was volume increase in specific left cerebellar areas. This increase was associated with reduced depressive symptoms.

Previous studies have demonstrated that ECT increases temporal gray matter volume and cortical thickness.[3] However, previous studies did not reveal cerebellar changes. Authors consider huge interindividual variability in cerebellar volumes and the defects in data normalization used in conventional whole brain templates as possible reasons for this disparity. Smaller sample size and the potential role played by psychotropic medications in the observed changes make any conclusions difficult. It is also likely that these changes are transient. However, this study adds to the growing interest in various brain stimulation therapies, including ECT in particular, and their positive effect on brain structure and function.

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NEW APPROACH TO TREAT BENZODIAZEPINE DEPENDENCE

Benzodiazepines are widely prescribed and a good proportion of long term users become dependent on them. Patients on high doses of benzodiazepines for

prolonged periods of time struggle to come off these medications. Initially demonstrated in 2002, intravenous flumazenil is a method of detoxification.[1] An Italian group has been using subcutaneous flumazenil for more than a decade; they highlight their experiences in the largest reported case series of subcutaneous treatment with flumazenil.[2] Adults on benzodiazepine dose exceeding 50 mg for over six months were treated with flumazenil subcutaneous infusion for seven days. An elastomeric pump (a small and light disposable medical device releasing a constant flow at 1.5 ml/hour) was used to release about 1 mg of flumazenil every 24 hours. Patients also received oral clonazepam every evening, at a dose starting from 5–6 mg on the first day and falling to 0.5–2 mg on the last day of flumazenil treatment. All patients received antiepileptic drugs for a period commencing 10 days prior to the admission and throughout the hospital stay.

Mean duration of benzodiazepine abuse reported in this series was nearly five years. Average equivalent daily dose was 389 mg. In 75% of them, benzodiazepines were medically prescribed to start with. Almost all patients reported previous unsuccessful attempts to reduce or discontinue these medications. Lormetazepam and lorazepam were the medications abused at very high dosages. Nearly a third of the patients experienced withdrawal symptoms during flumazenil treatment. Following discharge, two patients experienced convulsions despite being on anticonvulsants. 90% of patients were successfully detoxified with flumazenil treatment. Majority were discharged on low dose clonazepam. A telephonic follow up revealed that half of those contacted were not using any benzodiazepines. One in five patients have returned to high dose benzodiazepine use. Subcutaneous flumazenil assists rapid transition from very high dose dependence to none or low dose use. This case series show that subcutaneous flumazenil is an effective method for rapid detoxification from high dose benzodiazepines. Authors report that this treatment is particularly popular among doctors who are dependent on benzodiazepines.

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Source of support: None
Conflict of interest: None declared
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First submitted: 27th November 2016
Published online: 12th January 2017