A SELECTIVE SUMMARY OF PSYCHOPHARMACOLOGY RESEARCH PUBLISHED IN FIRST HALF OF 2015

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A glimpse of the psychopharmacology articles published in the first half of 2015 reveals an increasing emphasis on risk-benefit balance (Articles 2, 5, 8, 9, 10). Ten such articles that may help to expand our understanding, challenge our practices, and benefit our patients are summarized here. It is encouraging to learn that antidepressants reduce mortality in IHD (Article 2). Mortality in schizophrenia is reduced by antipsychotics when their doses are not high (Article 9). No new molecules have arrived on the scene, though few are on the pipeline. One exciting development is the renewed interest in glutamatergic system, with potential translation taking place into clinical application (Article 6). Parallel to our expanding knowledge base of the role of inflammation in mental disorders, benefits of anti-inflammatory agents are again being reviewed (Article 3). Challenges in treating bipolar depression are reiterated by poor remission rates and high dropout rates (Article 7).

1. CAN LITHIUM SUPPLEMENTATION REDUCE SUICIDE RATES?

A recent metaanalysis of secondary data collected during RCTs suggested that lithium could reduce suicide by 60-80% among patients receiving the molecule in therapeutic doses.[1] If lithium has anti-suicidal effects, would the same apply to lithium that naturally exists in drinking water too?

Many ecological studies have supported this idea. This has also led to a suggestion that we should perhaps aim for a minimum daily requirement of 1000 micrograms of lithium. One area of growing interest is the possible neuroprotective effects of lithium, triggered by the observation that bipolar patients on continuous lithium therapy are less likely to develop dementia than those who are not.[2] The recent study by Ishii et al. from Japan add to these interesting possibilities of lithium:[3]

They compared the standardized mortality rate (SMR) due to suicide in 274 municipalities in Japan's southernmost island, Kyushu. Lithium level in tap water samples from each municipality was also measured. Researchers checked whether lithium level predicted suicide SMRs, using multiple regression analysis, and found that total and male suicide SMRs were inversely associated with lithium levels. When social factors were taken to account, male suicide SMRs were still inversely associated with lithium levels. The mean level of lithium in

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water is very low compared to therapeutic doses — If one were to drink this water to substitute the 600 mg daily dose, an intake of 142857 L would be required!

The study is limited by lack of data relating to lithium levels in food and the general consumption habits of participants or localities. Moreover, the possibility of ecological fallacy looms large over this study design. Since suicide is a rare event, conducting trials with sufficient power to detect any effect is extremely difficult. However, ecological studies like this do help to generate hypotheses and widen the possibilities.

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3. Ishii N, Terao T, Araki Y, et al. Low risk of male suicide and lithium in drinking water. J Clin Psychiatry 2015; 76(3):319–26.

2. CAN ANTIDEPRESSANTS REDUCE MORTALITY IN ISCHEMIC HEART DISEASE?

Depression is an independent risk factor for mortality in Ischemic Heart Disease (IHD). Benefits of antidepressants on mortality in IHD are still debated due to conflicting results reported by studies. A seven-year follow-up study had revealed that, compared with those who are sufficiently treated, insufficient duration of antidepressant treatment is associated with a threefold increase in mortality.[1]

Krivoy et al. from Israel studied whether adherence to antidepressant therapy is associated with mortality in IHD.[2] Medical records of the largest service provider in Israel were retrospectively analyzed. Mortality information was collected for 63,437 subjects with IHD diagnosis who were prescribed antidepressants. Medication possession ratio (period in which medications were purchased, in relation to the total prescription period) was taken as the measure of adherence. Three- quarters of study population were over 65 years of age. Mean follow-up period was 27 months. It was found that 36% of the patients discontinued antidepressants within a month. 38% adhered well. Analysis showed that moderate and good adherence to antidepressants are associated with around 15% reduction in risk of death.

This study shows that, if individuals with IHD and depression adhere to the prescribed antidepressants, their risk of death is reduced. This effect remained even after adjusting for various confounding factors for mortality in this group like smoking status, age, gender, etc. It is not clear whether antidepressants produce these benefits by improving adherence in general to all medications for physical disorders, by improving healthy behaviour, or by direct cardiac benefits of improved mental health. Improving adherence to antidepressant treatment is likely to play an important role in reducing mortality in depressed individuals with IHD.

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3. ARE ANTI-INFLAMMATORY AGENTS USEFUL IN DEPRESSION?

Pro-inflammatory status is associated with depression.[1] Higher concentrations of certain inflammatory markers and increased activity of the COX 2 enzyme have been reported in depression. It is on this background that various anti-inflammatory agents are investigated for their antidepressant effect. Results of these studies are very contradictory, with some even suggesting that NSAIDs may actually reduce the benefit of SSRIs.[2]

Eyre et al. conducted a systematic review of all available evidence to see whether anti-inflammatory agents, either as a group or as specific subgroups, have any reliable antidepressant effect.[3] Eleven studies (seven RCTs) were included in the analysis. Four of the six RCTs on selective COX2 inhibitors showed significant antidepressant effects. Remaining two studies indicated effects that were not statistically significant. Heterogeneity in effect and variability in study characteristics limited any firm conclusions. Among the five studies on non-selective COX inhibitor NSAIDs, the only available RCT failed to show any significant effect. In summary, the effect of NSAIDs appears to be negligible. Clinical efficacy of these agents in depression, as monotherapy or as adjuvants, is not established.

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4. IS NALTREXONE EFFECTIVE IN NON-DEPENDENT HEAVY DRINKING IN YOUNG PEOPLE?

Naltrexone, an opioid antagonist, is an approved treatment for alcohol dependence. It can reduce both frequency and speed of drinking, and also offers the flexibility of 'as needed' use. These characteristics make it an attractive option for reducing heavy alcohol use among young people. O'Malley et al. report the results of the first adequately powered randomized clinical trial to test the efficacy of Naltrexone to reduce drinking among young adults.[1] This is a double blind, 2-group, parallel, placebo- controlled study. 140 young adults (18–25 years) who reported ≥ 4 heavy drinking days in the prior four weeks participated in this study. Individuals with severe alcohol dependence were excluded. Naltrexone or placebo was given for eight weeks. During the first week, participants were asked to take only one dose on a targeted basis at least two hours prior to a drinking situation. Daily dose was added in week two. Maximum daily dose of Naltrexone was 50 mg (25 mg daily + 25 mg as targeted use). Both groups received counseling.

Groups did not differ in percentage of heavy drinking days or abstinent days. Naltrexone significantly reduced the number of drinks per drinking day (naltrexone: mean = 4.90, SD = 2.28; placebo: mean = 5.90, SD = 2.51) ($p = .009$) and percentage of drinking days with estimated Breath Alcohol Concentration (BAC) ≥ 0.08 g/dL. Groups didn't differ in side effects.

Naltrexone is useful in reducing the intensity of alcohol use. Naltrexone group reported approximately one less drink per

drinking day, and they had 23% less days where BAC could have been above legal limits. The effects sizes reported are only modest. The study show that, though naltrexone may not be effective in reducing abstinent days, intensity of drinking can be reduced in young people who wish to reduce drinking.

Non-dependent heavy drinking is common. These individuals do not usually come to the attention of heath care providers. This group is more likely to accept moderation as a goal. This study shows that naltrexone can help non-dependent heavy drinkers to moderate their use. The effect size is modest, possibly due to the control group too receiving brief effective treatments along with the placebo.

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5. HOW COMMON ARE THE SIDE EFFECTS OF ANTIPSYCHOTICS?

Side effects are the major limitation of antipsychotics and significantly contribute to poor adherence. Since antipsychotics are generally prescribed for longer periods, identification and management of these effects are crucial.

Su Ling Young, Mark Taylor and Stephen M Lawrie conducted a systematic review to understand the prevalence of and management strategies available for nine main categories of antipsychotic side effects.[1] It is important to note that authors specifically excluded RCTs in favor of observational studies, as real world longer-term studies were considered to be best placed to provide answers to this question.

The commonest side effects were sexual dysfunction, metabolic problems and weight gain. Nearly 60% of men reported sexual dysfunction. All stages of sexual cycle were affected. Second Generation Antipsychotics (SGA) polytherapy was associated with more sexual dysfunction. Quarter to one third of women also reported sexual side effects. One third of all patients on antipsychotics experienced hyperprolactinemia. The highest rate was reported for amisulpride, and the lowest for clozapine.

Quarter to half of all patients receiving antipsychotics may be experiencing metabolic side effects. Clozapine and olanzapine are particularly associated with this. Prevalence of weight gain vary widely in studies (6-55%). Most studies suggest that olanzapine consistently causes weight gain, and that aripiprazole and ziprasidone are less likely to cause this problem. 15-50% of patients may develop antipsychotic-induced dyslipidemia.

The review did not have enough good quality studies to make distinctions between first and second generation antipsychotics. Effective treatments for the metabolic side effects, as concluded by this review, include nonpharmacological interventions like exercise, diet planning and group work (wellness program); and pharmacological interventions like statins. Lipid lowering therapies are less often utilized in this group of patients. The authors observe that scientific studies of adverse effects are seriously lacking. Baseline monitoring in clinical practice is poor. Authors suggest clinicians to regularly use a validated scale like Glasgow Antipsychotic Side-effect Scale (GASS) to improve early detection and implementation of appropriate interventions.[2]

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6. IS KETAMINE AN EFFECTIVE RAPID ACTING ANTIDEPRESSANT?

NMDA antagonist ketamine recently attracted significant interest due to its possible use as a rapid acting antidepressant. Since the first report in 2000, several groups have explored this potential.[1]

A group of Canadian researchers conducted a systematic review and metaanalysis of all randomized double blind placebo controlled studies of ketamine in depression.[2] The primary outcomes of interest were remission and response based on clinical rating scales. Seven studies met all their inclusion criteria. Ketamine was given as IV in all but one study which used intranasal ketamine. Common IV protocol was 0.5 mg/kg over 40 minutes. Saline was the common placebo.

The pooled OR was 7.06 (95% CI 2.50 – 19.95, $p < 0.001$) for clinical remission and 9.10 (95% CI 4.28 – 19.34, $p < 0.001$) for clinical response, both at 24 hours, indicating a significant difference in outcome favoring ketamine. After three days, the pooled OR was 3.86 for clinical remission and 6.77 for clinical response. After seven days, the pooled OR was 4.00 for clinical remission and 4.87 for clinical response. Effect sizes were larger for unipolar depression than bipolar depression. Majority of studies reported no serious adverse effects, though transient psychotomimetic symptoms were common.

The antidepressant response is rapid, but short lived. The effect may last up to one week. It is possible that ketamine may give a break from severe depression, especially where patients are immersed in total hopelessness or suicidal thoughts. This may give a window of opportunity to initiate/integrate other interventions.

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7. RESISTANT BIPOLAR DEPRESSION: ECT OR COMBINATION MEDICATIONS?

Bipolar depression is often difficult to treat. Combinations of medications, in various orders, are often attempted before ECT is considered as an option. Many guidelines, based on clinical experience and expert consensus, suggest ECT as a second line treatment for bipolar depression. No randomized controlled trials of ECT in treatment of bipolar depression have been reported.

Schoeyen et al., from Norway, conducted the first RCT of ECT against algorithm-based pharmacotherapy in treatment resistant bipolar depression.[1] Primary outcome measure was MADRS scores at six weeks. This was a multicenter study with 73 patients. Psychiatrists treating these patients had to agree that patients met the clinical indications for ECT. Medication resistance was defined as lack of response to two trials with antidepressants and/or mood stabilizers with documented efficacy in bipolar depression (lithium, lamotrigine,

quetiapine, or olanzapine). Rapid cyclers were excluded. ECT was given as right unilateral brief pulse stimulation, three times a week, with a maximum of 18 sessions. Medication algorithm was agreed for each patient prior to randomization. Treating doctors or patients were not blinded to assignment.

ECT group received 10 stimulations on average. Almost all patients in the medication group were on combination treatments. The mean MADRS score at six weeks was 6.6 points lower in the ECT group (SE=2.05, 95% CI=2.5–10.6, p=0.002). Response rate was 74% in ECT completers, as compared to 35% in medication group. There was no difference in remission between the groups (35% vs. 30%).

ECT is more effective than pharmacological treatments in the acute phase. The response rate in this study is similar to that observed in unipolar depression. High dropout rates and relatively small sample size limit the statistical power to detect differences between groups. Most severely depressed patients were not included in the study because of their inability to give informed consent or their psychiatrists' opinion that they were in urgent need of ECT. The low remission rates highlight the ongoing difficulties in treating bipolar depression.

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8. SHOULD WE USE THE BENZODIAZEPINES LESS?

Gagé et al. recently published a study showing that long-term (>3 months) Benzodiazepine (BZ) use is associated with an increased risk of developing Alzheimer's Dementia (AD) in the elderly.[1] Long-term use, especially of long half-life BZ, was particularly problematic in this group. They had sampled subjects dating six years back before they received a dementia diagnosis.

However, there are many alternate explanations. It is possible that mild cognitive impairments (MCI) or other prodromal manifestations of dementia may have triggered the prescription of BZ. Use of alcohol and anticholinergic medications was not controlled in this study. It is also argued that stress and anxiety itself may contribute to neuronal damage; and that BZs may in fact help to reduce such effect. Early cortical changes may cause poor sleep and anxiety, and this may be forcing the subjects to seek anxiolytic medications. However, even those who point out limitations like this too agree that it would be better if we prefer the lowest possible dose of BZs, that too of short half-life agents. Most guidelines support only short periods of use, that too after the failure of non-pharmacological methods.

Another study looked at use of BZ in schizophrenia.[2] This systematic review reveals that BZs are superior to placebo in short-term use for global, psychiatric and behavioral outcomes. As expected, they are inferior to antipsychotics in longer-term outcomes. Authors conclude that the evidence is conflicting, and that BZ use should be limited in this group.

A retrospective descriptive analysis of BZ prescription in USA by Olfson et al. adds another dimension to the above finings.[3] 5.2% of the US population used BZ in the study year. This proportion increased with age, and 8.7% were using BZ in 65-80 years group. Use was twice as common among women. One third of the use was classified

as long term (more than four months) in the elderly group. Quarter of all prescriptions was for long acting agents.

An editorial in JAMA Psychiatry argues that BZs should be regulated as controlled substances.[4] Short-lived nature of benefits, dependency potential, association with falls, and contributing role in motor vehicle accidents are listed as reasons for this position. Several thousand deaths are attributed to BZs every year. The authors remind us that BZs should be used only for acute episodes of insomnia or transient anxiety in young persons, that too for the shortest possible duration. The recommendation to psychiatrists to restrict prescription of BZs sounds appropriate, given the increasing concern about misuse and harm associated with them.

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9. DO ANTIPSYCHOTICS INCREASE MORTALITY?

Patients with schizophrenia, on average, die 10-20 years earlier than the general population. Would antipsychotics, through their adverse effects, be contributing to this excess mortality? Dose related sudden cardiac death with antipsychotics is well known. There are suggestions that long-term use of antipsychotics may be associated with increased mortality in general. On the other hand, large prospective studies have also shown that antipsychotics may in fact reduce mortality.

Torniainen et al. conducted a prospective population based cohort study of individuals with schizophrenia.[1] All individuals in Sweden diagnosed with schizophrenia before 2006 (n = 21,492) and belonging to the age group 17–65 years, and persons diagnosed with first-episode schizophrenia in 2006–2010 period (n = 1,230) were studied. Mortality rates for both the groups were studied for the period between 2006 and 2010. For each person with schizophrenia, 10 age and sex matched persons without the illness were included in the control group. Prescription and mortality data were collected from respective national registers.

Antipsychotic dose was classified as high if it was 1.5 times above the daily defined dose (DDD). (DDD is the assumed average maintenance dose, and is often less than the maximum daily dose. For example, DDD of olanzapine is 10 mg, whereas its recommended maximum daily dose is 20 mg.)

Their findings revealed that 7% of the schizophrenia patients died during the 5-year follow-up. The corresponding figure among controls was 1.6%, resulting in a hazard ratio (HR) of 4.8 (95% CI: 4.5–5.1) for schizophrenia. In both chronic and first episode groups, those not on antipsychotics had higher mortality.

This is the first study to investigate how the cumulative exposure to antipsychotics affects the excess mortality seen in schizophrenia. The highest risk of death was among patients with no antipsychotic use. Both high antipsychotic and no antipsychotic groups had higher cardiovascular mortality. Mortality rates

among women on larger doses of antipsychotics were higher, supporting previous reports which suggest that women, on average, experience more side effects. This has led to the idea that perhaps women may require smaller doses only. This study concludes that patients with low or moderate antipsychotic exposure have substantially lower overall and cardiovascular mortality than patients with no or high exposure. These findings are limited by the fact that this is an observational study where we could not attribute causality.

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10. IS MINDFULNESS BETTER THAN ANTIDEPRESSANTS?

Maintenance therapy with antidepressants (AD) is recommended for at least two years for individuals with recurrent depressive disorder. Adherence to AD is often poor, and many patients wish to discontinue medications sooner, even though it is likely to lead to relapse. Mindfulness Based Cognitive Therapy (MBCT) is known to reduce rates of depressive relapse or recurrence when compared to usual care or placebo. For those patients who wish to come off AD, would MBCT be an evidence-based option?

Kuyken et al. recruited adult patients with recurrent depressive disorder from general practices in UK, to test whether MBCT-TS (MBCT with support to taper or discontinue AD treatment) was better than maintenance AD in prevention of depressive relapse or recurrence over two years.[1] Patients with current depression, past or present psychosis, bipolar disorder, or substance use disorders were excluded. Participants were randomly allocated to either maintenance AD treatment or an 8-week MBCT program that included support to taper or discontinue their maintenance AD medication (MBCT-TS). (MBCT is a manualized, group-based skills training program designed to enable patients to learn skills that prevent the recurrence of depression. Mindfulness practices and cognitive-behavioral skills are strengthened, both in session and through homework assignments.)

The MBCT group received eight group sessions, normally over consecutive weeks, with four refresher sessions offered roughly every three months for the following year. Patients in the maintenance AD group received support from their general practitioners to maintain therapeutic levels of the medications. Relapse or recurrence was defined as an episode meeting DSM-IV criteria for a major depressive episode.

424 patients were randomized to the above groups. Baseline characteristics were balanced between the two groups. Analysis of the primary outcome showed no evidence of a reduction in the hazard of relapse or recurrence with MBCT-TS compared with maintenance AD treatment. The time to relapse or recurrence of depression did not differ between the groups over 24 months. Almost 50% experienced relapse in both the groups.

Participants were recruited by methods including general invitation. Hence, this sample may be different from those who consult primary care physicians or psychiatrists for options regarding maintenance treatment. Participants were aware of treatment allocation. In the AD group, 24% did not adhere to therapeutic doses of medications. 29% in the MBCT group were still on ADs. This lack of

control over the use of ADs further limits the interpretation of this study.

This study shows that MBCT-TS is not superior to maintenance ADs over two years of follow-up for patients with recurrent depression. For vast majority of patients, AD maintenance is still the most effective treatment for preventing relapse.

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