Volume : 3 | Issue : 5 | May 2014 • ISSN No 2277 - 8179

Research Paper

# Optimizing cognitive functionality in severe mental illness. An evidence-informed medicine clinician primer

Medical Science

**KEYWORDS :** Psychiatry, Cognition, Psychopharmacology, Mental health

**Dr Joel Lamoure RPh** — Departments of Psychiatry and CPD, Western University, London, ON Canada

**DD. FASCP** — Lawson Health Research Institute, London, ON Canada

## ABSTRACT

*Cognition involves a series of mental activities such as seeing, attention, memory, reasoning, and problem solving and is integral to the well being of patient care and assessment. There are a variety of mental health conditions, including schizophrenia, bipolar disorder and affective disorders that can diminish a patient's ultimate goal of functionality. Functionality, which is integrally linked to cognition, covers the individual's ability to engage in daily activities. Inability to have "clarity of thought" inherentlyturns the patient to forms of self-medication in order to advance cognition (eg: smoking) and miss medications. As medication use is the cornerstone of psychiatric interventions, selection of agents utilizing receptor affinities, patient history/response, co-morbidities and unique dosing formulations (eg: long-acting injectable) that enhance cognition should be optimized. This paper is designed to provide a primer for clinicians to optimize adherence, medication selection and identify/monitor cognitive changes in their patient population from a question-based, narrative approach.*

### 1. What Is Cognition And Why Is It Important?

Cognition involves a series of mental activities such as seeing, attention, memory, reasoning, and problem-solving.[1, 2] Cognition also determines one's ability to process information, as well as the speed at which one can process information.[1,2] More specifically, cognitive processes in the brain involve receiving and transmitting information and then processing the information to perform specific tasks and operations.[2] When combined, all of these cognitive functions play an important role in our ability to carry out activities of daily living, work, manage finances, and interact socially with others; as such, they impact our overall personality and functionality.[1,2] Therefore, any level of cognitive impairment may significantly impact one's ability to function within society and carry out the activities necessary to live independently.[1]

In addition to overall functioning, cognition is also critical for assisting patients with medication adherence.[1] Non-adherence to one's medication regimen may result in deterioration of the original mental health condition or the increased risk of relapse in those patients who have successfully achieved remission.[1] Moreover, healthy cognition can help individuals to identify new-onset medical problems and have them addressed early, before they worsen other comorbidities or cause permanent damage.[1] Finally, as alluded to above, cognition is critical to enabling an individual to work, function in society, and live independently.[1] Therefore, the development of cognitive impairment may lead to increased financial burden for the patient and caregivers, due to the loss of ability to live independently, as well as the loss of productivity for the patient and his/her caregivers.[1]

### 2. What Disease States and Medications Negatively Impact Cognition?

**Table 1. Disease states that negatively impact patient cognition**

| Disease States that Negatively Impact Cognition[3,4] |
|---|
| Alzheimer's Disease |
| Dementia |
| Delirium |
| Insomnia |
| Psychosis |
| Schizophrenia |
| Bipolar Disorder |
| Major Depressive Disorder |
| Post-traumatic Stress Disorder |
| Multiple Sclerosis |
| Stroke |
| Traumatic brain injury |
| Hypertension (taxing the physiological integrity of the brain and affecting cognitive reserve) |
| Heart Disease (taxing the physiological integrity of the brain and affecting cognitive reserve) |
| Diabetes (taxing the physiological integrity of the brain and affecting cognitive reserve) |
| HIV (taxing the physiological integrity of the brain and affecting cognitive reserve) |
| Chronic fatigue syndrome |
| Lupus |
| Cancer |
| Advanced aging |

**Table 2. Medications that negatively impact patient cognition**

| Medications that Negatively Impact Cognition [3,4] | Reason |
|---|---|
| Anticholinergics (excluding tricyclic antidepressants) | |
| First generation antihistamines (e.g., diphenhydramine, chlorpheniramine, hydroxyzine, promethazine) | · Great risk of confusion<br>· Clearance reduced with advanced age |
| Antiparkinsonian agents (e.g., benztropine) | |
| Antispasmodics (e.g. scopolamine, belladonna alkaloids) | |
| Central Nervous System Acting Drugs | |
| Tricyclic antidepressants (e.g. amitriptyline, imipramine, clomipramine) | · Highly anticholinergic – therefore, great risk of confusion, and clearance reduced with advanced age<br>· Sedating<br>· Impaired psychomotor function |
| Selective serotonin reuptake inhibitors (e.g., sertraline, paroxetine, fluoxetine, citalopram, escitalopram) | · Impaired psychomotor function<br>· Possibly sedating<br>· May have anticholinergic effects – therefore, great risk of confusion |

Volume : 3 | Issue : 5 | May 2014 • ISSN No 2277 - 8179

| | |
|---|---|
| Antipsychotics (typical and atypical agents) | · Sedating<br>· CNS effects<br>· Increased risk of cerebral vascular accident (stroke) in patients with pre-existing dementia<br>· Impaired psychomotor function<br>· Anticholinergic – therefore, great risk of confusion, and clearance reduced with advanced age |
| Anticonvulsants (e.g., phenytoin, carbamazepaine) | · Impaired psychomotor function |
| Antimuscarinics (e.g., oxybutynin, tolterodine, folifenacin) | · Anticholinergic – therefore, great risk of confusion, and clearance reduced with advanced age |
| Barbiturates (e.g. phenobarbital, secobarbital) | · Sedating |
| Benzodiazepines (e.g., lorazepam, diazepam, clonazepam, oxazepam, temazepam) | · Increase risk of cognitive impairment, delirium<br>· Sedating<br>· Impaired psychomotor function<br>· Clearance of long-acting agents reduced with advanced age |
| Chloral hydrate | · Sedating |

| Other Medications that Negatively Impact Cognition[3,4] | Reason |
|---|---|
| Non-benzodiazepine hypnotics (e.g., zolpidem, eszopiclone) | · Increase risk of cognitive impairment, delirium<br>· Sedating<br>· Impaired psychomotor function |
| Oral decongestants (e.g., pseudoephedrine, phenylephrine) | · Confusion<br>· Hallucinations<br>· Impaired psychomotor function<br>· Insomnia |
| Analgesics | |
| Opioid analgesics (e.g., pentazocine, meperidine, morphine, hydromorphone, oxycodone) | · Confusion, hallucinations |
| Skeletal muscle relaxants (e.g., cyclobenzaprine, methocarbamol) | · Highly anticholinergic – therefore, great risk of confusion, and clearance reduced with advanced age<br>· Sedating |
| Gastrointestinal Drugs | |
| $H_2$-receptor antagonists (e.g., ranitidine, famotidine) | · Induce or aggravate delirium in older adults |
| Hormonal Drugs | |
| Corticosteroids (e.g., prednisone) | · Induce or aggravate delirium in older adults<br>· Can induce psychosis |
| Other Drugs | |
| Chemotherapy | · Severe memory loss<br>· Confusion<br>· Disorientation |
| Polypharmacy (5 or more medications) | · Due to reduced liver and kidney function, the body has problems fully processing medication à impairs brain health and cognitive reserve |

**3. How do we Measure Cognition?**

Assessing and evaluating a patient's cognitive function is important, as it informs patients and their families about potential functional limitations.[5]Executive functioning is an over-reaching term that denotes a patient's ability to complete tasks that have relevance in the domains and sub-domains of cognition. The executive functions include: problem solving, planning through to completion of a task, organizational skills, attention for selected activities and short term memory.[6] Moreover, abnormal results of various cognitive tests may prompt physicians to more aggressively assess their patient so that early treatment may be started to prevent continued cognitive deterioration.[3]

High level executive testing may be employed to assess cognition and integrate together the many subsets of logistics, reasoning, activity and cognition that go into the completion of everyday processes.

**Delis–Kaplan Executive Function System[7]:**

This complete neuropsychiatric test is designed to assess nine different subdomains that together make up executive functioning. The Trail Making Test measures the patient's flexibility of thinking on a visual-motor sequencing task. A Verbal Fluency Test measures letter fluency. The Design Fluency Test measures one's initiation of problem-solving behavior while understanding the rules and risks inherent with the assigned activity. Other tests include a Color-Word Interference, Sorting, Twenty Questions, Word Context, Tower Test and Proverb Test.

Together, these 9 domains address all the patients cognitive ability to do higher level executive processes and test verbal, non-verbal, Judgement, recall, feedback ability, integration of information, deductive reasoning and flexibility of thinking.

**Verbal Fluency Test[8]:**

The most commonly used type of verbal fluency test is the category (or semantic) fluency test. This test allows the patient 60 seconds to name as many items as possible within a specific category (e.g., animals). A score of greater than 15 is considered normal, while a score of less than 15 suggests dementia. Overall, the verbal fluency test helps clinicians to identify patients with mild cognitive impairment, as abnormal results may be detected by this test prior to any other cognitive test. However, the test has educational bias and, unfortunately, provides clinicians with no insights into the patient's specific deficits.

**The Clock Drawing Test[8]:**

This cognitive test is a quick way by which a clinician can assess and evaluate a patient's ability to organize and plan. During this test, the patient is given a blank sheet of paper and told to draw the face of a clock with all its numbers, and then set the time to 10 minutes past 11. While this test has been well studied and validated, there is unfortunately no consensus on how to score it. To make the evaluation as simple for the clinician as possible, the test can be scored as 'normal', in which the clock is correctly drawn with the accurate time, or 'abnormal', in which at least one problem with the clock has been identified.

**The Mini-Cognitive (Mini-Cog) Assessment Instrument[8]:**

The Mini-Cog lacks the educational bias of the verbal fluency test. This test combines a clock-drawing test with a three-item recall test. Specifically, the patient is asked to repeat three unrelated words, complete the clock drawing test, and then recall the three initial words. The test should take approximately two to four minutes to complete.

Scoring on the test ranges from 0 to 5, with one point assigned for each correctly recalled word (on delayed recall) and two points if the clock is drawn correctly. A score between 0 and 2 suggests dementia and a score of 3 to 5 indicates a low probability of dementia.

**Mini-Mental State Examination (MMSE)[8]:**

This 30-question test assesses the patient's orientation, attention, concentration, memory, language, and construction abilities. As this test examines multiple domains, it is useful for de-

termining specific deficits that the patient is experiencing. As such, the MMSE is considered the cornerstone of a complete cognitive assessment and is the most widely used cognitive test. The entire test usually takes about 12 minutes, though persons with cognitive deficits may require appreciably longer. Similar to the verbal fluency test, an educational bias exists. The total result is out of 30, and the interpretation of the test (most commonly used in dementia and Alzheimers) is as follows[9]:

Greater than or equal to 25 points: Normal cognition.
19-24 points: Mild cognitive impairment
10-18 points: Moderate cognitive impairment
≤9 points: Severe cognitive impairment

**The Montreal Cognitive Assessment (MoCA):**
The MoCA test is designed to detect mild cognitive impairment and Alzheimer's disease.[5,10] The MoCA also overcomes many of the documented limitations of the MMSE.[5,10] In patients with a history of transient ischemic attack or stroke, the MoCA is preferred over the MMSE because the MoCA test has a stronger evaluation of executive dysfunction.[5] In addition, the MoCA provides a much more comprehensive assessment of various cognitive domains, such as short-term memory (delayed recall test), language (verbal fluency test; item naming task), visuospatial abilities (clock drawing test), attention, concentration, working memory, and temporal and spatial orientation.[10] Like the MMSE, the one page, 30-point MoCA test can often be completed in approximately 12 minutes.[5,10]

**Confusion Assessment Method[8]:**
The Confusion Assessment Method (CAM) consists of an instrument and diagnostic algorithm that was developed in 1990 to enhance the ability of non-psychiatric clinicians to diagnose delirium quickly and accurately after a short, yet formal, cognitive test. In order to accomplish this, the CAM instrument assesses the presence, severity, and fluctuation of specific delirium features:

- Acute onset
- Inattention
- Disorganized thinking
- Altered level of consciousness
- Psychomotor agitation or retardation
- Altered sleep-wake cycle

**The diagnostic algorithm consists of four fundamental features of delirium:**
1. Acute onset and fluctuating course
2. Inattention
3. Disorganized thinking
4. Altered level of consciousness

To diagnose delirium using this tool, the patient must demonstrate features 1, 2 and either 3 or 4. The CAM tool has a sensitivity of 94% to 100% and specificity of 90% to 95%.[11]

**4. Which Receptors Are Implicated in Cognition?**
**The receptors that are implicated for impacting cognition are as follows:**
- GABA[12]
- 5-$HT_6$[13]
- 5-$HT_7$[12]
- 5-$HT_{7A}$[14]
- 5-$HT_{2A}$[12]
- 5-$HT_{2C}$[12]
- 5-$HT_{1A}$[12]
- 5-$HT_{1C}$[14]
- $H_1$ receptors[12]
- $H_3$ receptors[12]
- Acetylcholine nicotinic receptors[15]
- Acetylcholine muscarinic receptors (muscarinic $M_1$)[12]
- $D_1$[16]
- $D_2$[12]
- $D_3$[12]
- NMDA receptors [12]
- Metabotropic glutamate receptors (mGluRs)[12]
  - o mGluR2[12]
  - o mGluR3[12]
- Glycine site on the NMDA receptor[12]
- Adrenergic receptors[12]
  - o $\alpha_1$ receptors[12]
  - o $\alpha_2$ receptors[12]

To date, studies of psychiatric disorders have traditionally focused on measurable psychiatric or emotional symptoms like depression, anxiety, mania, and positive symptoms like psychosis. However, cognitive deficits may severely compromise quality of life and impair patient functionality. [12,17]

**5. What Are the Costs of Non-Adherence?**
Non-adherence to medications has significant costs associated with it, both financial and pertaining to patient outcomes. In patients with schizophrenia, lack of adherence to medication has been estimated to cause at least 50% of relapses.[18,19] In terms of increasing the risk of relapse, it has been found that approximately 75% of schizophrenia patients who are non-adherent over a five-year period will relapse, versus only 35% of patients who are adherent.[19] Each individual relapse episode has been estimated to cost between $10,000 and $26,000.19 The majority of these costs stem from hospitalizations, since hospital stays for treatment of a relapse are approximately 2.5 times longer in a non-adherent than adherent schizophrenia patient (averaging 38.1 vs. 14.3 days).[18]However, it is important to remember that, in addition to whatever financial costs there are, it becomes increasingly harder for a patient to achieve remission with each subsequent relapse.[18]

In addition to concerns about relapse, additional patient costs include a four-fold increased risk of suicide and an approximately 40% increase in alcohol and substance use in patients with schizophrenia who are non-adherent to their treatment regimen.[18,20] Moreover, non-adherent patients with schizophrenia are thought to be twice as likely to be violent, arrested, or victimized than those who are adherent.[20] An additional financial cost of non-adherence to the health care system is the observed approximately 50% increase in emergency psychiatric service usage.[20]

While the above examples show how non-adherence results in significant financial and human costs for patients with schizophrenia, it is important to recognize that similar costs apply to any patient population in whom non-adherence to a medication regimen exists. For example, in healthy elderly patients, increased costs in medication-non-adherent individuals have been identified related to increased hospitalizations and medication side effects related to drug misusage.[21]For example, in one study of 2169 elderly patients living in the community, 12.6% of all emergency room visits were drug-related, accounting for $1.5 million in direct health care costs over a 12-week period.22

Therefore, it is important to recognize that non-adherence to one's medication regimen can have significant implications for patient outcomes, and can add further to already significant financial burdens for both the patient and healthcare system.

**6. How Does Cognition Impact Adherence?**
The definition of patient compliance is "the extent to which a person's behavior coincides with the medical advice he/she has received".[23] Poor compliance is often defined as adhering to less than 70% of the medications prescribed over the last week.[24] Several observational studies have demonstrated that baseline cognitive abilities significantly impact medication adherence.[25] This is because adherence requires complex cognitive skills, like accessing medications, understanding prescribed directions, scheduling and adjusting medications according to daily activities, having continuous access to medications via refills, and being able to determine what to do when a dose is missed.[26] In addition to requiring complex cognitive skills, there also is evidence that memory deficits can result in decreased ability to appropriately manage one's medications.[4]

Volume : 3 | Issue : 5 | May 2014 • ISSN No 2277 - 8179

Given that psychiatric conditions develop due to changes in brain neurotransmitters and/or brain matter, cognitive function is often affected. For example, in patients with schizophrenia, common symptoms include delusions, hallucinations, disorganized speech, deficits in speech and language, impaired recognition memory, and frank cognitive impairment.[27] As a result of these symptoms, it can be challenging for schizophrenic patients to manage their complex medication regimens.[27] Therefore, adherence to medications is greatly influenced by the schizophrenia itself and the cognitive impairment that results from the disease.[29] Given this, it may be difficult for patients to take their daily medication (e.g., oral atypical antipsychotics); as such, cognitive function may not improve with medication.[29] More specifically, patients with schizophrenia may forget to take their medication, stop their medication without being instructed to do so, or take their medication in a different way than it was initially prescribed.[29] In order to overcome this, it may be helpful for patients to take long-acting antipsychotics to eliminate their need to remember medication and administration instructions on a daily basis.[29]

Lack of insight/cognitive impairments in a patient with schizophrenia also greatly impacts compliance and is thought to be one of the major factors influencing non-adherence in this patient population.[29] This lack of insight often leads patients to think that their condition does not warrant treatment or, alternatively, that if symptoms improve, they no longer need to take their medication.[29] Such beliefs may destabilize the patient and lead to negative outcomes.[29]

In addition to lack of insight, patients who feel persecuted may also be reluctant to take their medication, as will those who erroneously fear that the medication will poison them.[29]

Finally, patients with schizophrenia or schizoaffective disorder and cognitive impairment (e.g., attention, functionality and memory deficits) may also have poor medication adherence because they forget the timings or doses of their medications.[30] In fact, in one prospective study, being a first-episode schizophrenia patient with poorer pre-morbid cognitive function was a predictor of antipsychotic non-compliance.[30]

**7. What Cognition Enhancers Are Currently Available?**

To date, no cognition enhancers currently are indicated for the cognitive deterioration often seen in patients with schizophrenia or other psychoses like bipolar disorder. However, a handful of drugs target various forms of dementia.

One of the most common forms of dementia is Alzheimer's Disease (AD).[31] AD impacts patients and families greatly due to the irreversible and progressive decline in memory and reasoning that is virtually inevitable.[31] In the early stages, patients often present with minor difficulties recalling new information.[32,33] As the disease progresses, patients experience a gradual deterioration of memory and spatial orientation.[32,33] Changes in personality, mood, and behavior also develop, as well as a decreased ability to function on a daily basis.[32,33] In general, a decade after the initial diagnosis, Alzheimer's patients often have lost many of their basic functions (e.g., motor control) and require constant care and assistance in an institution.[31,34] Tragically, AD and other forms of dementia represent the sixth highest cause of death in the United States and cost the United States economy approximately $183 billion dollars per year.[31]

Unfortunately, no medication is currently available that will stop or reverse Alzheimer's disease progression that has already occurred. In Canada, four medications have been approved for the treatment of AD in attempts to reduce symptoms: an NMDA receptor antagonist (memantine) and three cholinesterase inhibitors (ChEIs) (donepezil, galantamine, and rivastigmine). In the United States, another ChEI, tacrine, has been approved. Tacrine, however, is rarely used and not approved in Canada due to its questionable efficacy and the significant risk of hepatotoxicity associated with its use.

The approved medications primarily improve symptoms, though they also have been demonstrated to have a modest positive impact upon global function, cognition, and activities of daily living.[31] More specifically, while donepezil is indicated for treating all stages of AD, rivastigmine and galantamine are indicated to treat mild to moderate AD and memantine for moderate to severe AD.[31] Overall, the evidence in the literature to date does not demonstrate that one medication is more effective than any other.[31]

None of the currently-available medications specifically target the proposed pathophysiology of AD, like the amyloid and tau hypotheses by which protein aggregates form in the brains of patients with AD.[31]More specifically, the amyloid and tau hypotheses are thought to explain the development of regional neurodegeneration, subsequent cognitive decline, and neuropsychiatric disturbances.[31] These proposed disease pathways are still being investigated, as well as a number of drugs with mechanisms connected to two pathways (e.g., targeting amyloid-b proteins and tau pathology).[31] Other drugs currently under development and investigation target pathways involved in neuroinflammation, mitochondrial dysfunction, and neuroprotection.[31]

**8. What Is The Atypical Antipsychotics Role In Potentially Improving Cognition For Mental Health Patients?**

If we consider this answer from the perspective of receptor affinities, the receptor "fingerprint" of each molecule may provide some degree of insight into the efficacy of the medication on cognition. While this is not an exact science, and the correlation between efficacy and receptor affinity is not exactly 1.0, this concept still provides the clinician a starting template to assess medication use. [35,36]

Adverse effects do monitor closer in correlation to the receptor affinities, but as we start to look to enhancing cognition, the balance of affinity and efficacy, plus clinical experience starts to balance out. Table 3lists some of the more common receptors implicated with antipsychotics and cognition as well as the affinity constants for the atypical antipsychotics in Canada at the time of writing. While the affinity constant is part of the equation and arguably the most important component of the mediation of the efficacy, one clinically cannot discount the dissociation constant as well. The Kd, or dissociation constant will advise the clinician of how long the medication stays in contact with the relevant receptor. [35,36]

**The clinical impact of the most common receptors in mental health is as follows[37]:**

Dopamine D2: Antipsychotic activity- Improve cognition through symptom control
Dopamine D3: Aid in decreasing addictive reward/improve cognition
Serotonin 5HT2a: Antipsychotic/mood/attenuate extrapyramidal symptoms (EPS)
Serotonin 5HT2c: Mediating attention, motivation, cognition, and reward processes
Serotonin 5HT7: Improve mood/cognition
Alpha1: Orthostatic hypotension/sedation/impair cognition
Alpha2c: Improve mood/cognition
Histamine H1: Impair cognition/sedation/weight gain
Acetylcholine Muscarinic M1: Impair Cognition

**Table 3.Common Cognition Receptors and Atypical Antipsychotic Affinities ($K_i$)[12,35-43]**

| Drug/ Receptor | D2 | D3 | 5HT2a | 5HT2c | 5HT7 | Alpha1 | Alpha2c | H1 | M1 |
|---|---|---|---|---|---|---|---|---|---|
| Clozapine | + | + | +++ | ++ | ++ | +++ | ++ | +++ | +++ |
| Olanzapine/ LAI | ++ | ++ | +++ | ++ | + | ++ | + | +++ | +++ |
| Paliperidone/ LAI | +++ | +++ | ++++ | ++ | +++ | +++ | ++ | ++ | - |
| Quetiapine | + | + | + | + | + | +++ | + | +++ | + |
| Risperidone/ LAI | +++ | +++ | ++++ | ++ | +++ | +++ | ++ | ++ | - |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Ziprasidone | +++ | +++ | ++++ | ++++ | +++ | +++ | + | + | - |
| Lurasidone | +++ | ? | +++ | 0 | ++++ | ++ | 0 | -/0 | - |
| Asenapine | +++ | ++++ | ++++ | ++++ | ++++ | +++ | +++ | +++* | - |
| Aripiprazole/ LAI | +++PA | +++ | +++ | ++ | +++ | ++ | ++ | ++ | - |

**Symbols refer to binding affinity (Ki):**
**Over 1000nM: Minimal or no receptor affinity: -/0**
100-1000nM: +
10-100 nM: ++
1-10nM: +++
<1nM: High receptor affinity: ++++
Legend: * Also acts as an H2 antagonist
PA: Partial Agonist
0: No listed affinity
?: Unknown
LAI: Long Acting Injectable Formulation (USA and/or Canada)

**9. Conclusion**

Impaired cognition results from mental health disorders, resulting in reduced adherence and ultimately leads to relapse and entrenchment of therapeutic failure and neurobiological changes and proposed treatment resistance.

As medication use is the cornerstone of psychiatric interventions, selection of agents utilizing receptor affinities, patient history/response, co-morbidities and unique dosing formulations (eg: long-acting injectable) that enhance cognition should be optimized. Patient and clinician preference is often weighted towards the long acting injectable format, currently with a higher uptake in Europe, compared to North America.[44,45]

However the results of using this dosing formulation, combined with positive cognition enhancement, is yet to be studied. Atypical antipsychotics are indicated in not only schizophrenia, but also the breadth of the affective spectrum, depending on the psychotropic employed. Use of receptor affinities and cognitive testing may allow clinicians to optimize patient outcomes using appropriate medication selection at the initiation of therapy.

Consideration of the medication fingerprint and delivery systems in a patient centric approach, optimizing motivational interview and patient-centered goals may reduce relapse, remission and non-reversible neurobiological changes in patients with severe mental illness.[46-48]

**Acknowledgements**

The author wishes to acknowledge the editorial, semiotics and clinical review contributions to this paper of Science Right Inc., Dr K.P. White and Professor Jessica C. Stovel.

**Disclosures/ Conflicts of Interest**

EIM-CARE Inc. has received unrestricted grant funding, utilized for creation and publication of evidence-informed scientific reviews from Janssen-Ortho Canada, Lundbeck Canada and Sunovion Canada.

Joel Lamoure has received lifetime research, speaking or grant funding from Janssen-Ortho Canada, Pfizer Canada, Pfizer Global, Astra-Zeneca Canada, Shire Pharmaceuticals Canada, Eli Lilly Canada, Valeant Canada, Otsuka Canada, Bristol-Meyers Squibb Canada, Lundbeck Canada and Sunovion Canada.

## REFERENCE

[1] Keefe RS, Harvey PD. Cognitive impairment in schizophrenia. Handb Exp Pharmacol. 2012;(213): 11-37. | [2] Cognifit. 'Cognition and the Cognitive Science.' http://www.cognifit.com/cognition. Accessed February 28, 2013. | [3] American Geriatrics Society 2012 Beers Criteria Update Expert Panel. American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc. 2012 Apr;60(4):616-31. | [4] Vance D, Larsen KI, Eagerton G, Wright MA. Comorbidities and cognitive functioning: implications for nursing research and practice. J Neurosci Nurs. 2011 Aug;43(4):215-24. | [5] Mai LM, Oczkowski W, Mackenzie G, Shuster A, Wasielesky L, Franchetto A. et al. Screening for cognitive impairment in a stroke prevention clinic using the MoCA. Can J Neurol Sci. 2013 Mar;40(2):192-7. | [6] Morgan, A. B., Lilienfeld, S. O. (2000). "A meta-analytic review of the relation between antisocial behaviours and neuropsychological measures of executive function". Clinical Psychology Review20 (1): 113–136 | [7] Delis, D. C., Kaplan, E., & Kramer, J. H. (2001). Delis-Kaplan executive function system (D-KEFS). Psychological Corporation. | [8] Simmons BB. Hartmann B, Dejoseph D. Evaluation of suspected dementia. Am Fam Physician. 2011 Oct 15;84(8):895-902. | | [9] Mungas D. In-office mental status testing: a practical guide. Geriatrics 1991. 46 (7): 54–8, 63, 66 | [10] Freitas S, Simoes MR, Alves L, Duro D, Santana I. Montreal Cognitive Assessment (MoCA): validation study for frontotemporal dementia. J Geriatr Psychiatry Neurol. 2012 Sep; 25(3): 146-54. | [11] Wei LA, Fearing MA, Sternberg EJ, Inouye SK. The Confusion Assessment Method: a systematic review of current usage. J Am Geriatr Soc. 2008 May; 56(5): 823-30. | | | [12] Kim DH, Stahl SM. Antipsychotic drug development. Curr Top Behav Neurosci. 2010;4:129-39. | [13] Meffre J, Chaumont-Dubel S, Mannoury la Cour C, Loiseau F, Watson DJ, Dekenye A, et al. 5-HT(6) receptor recruitment of mTOR as a mechanism for perturbed cognition in schizophrenia. EMBO Mol Med. 2012 Oct;4(10):1043-56. | [14] Meneses A. 5-HT system and cognition. Neurosci Biobehav Rev. 1999 Dec;23(8):1111-25. | [15] Takahashi H, Yamada M, Suhara T. Functional significance of central D1 receptors in cognition: J Cereb Blood Flow Metab. 2012 Jul;32(7):1248-58. | [16] Timmermann DB, Sandager-Nielsen K, Dyhring T, Smith M, Jacobsen AM, Nielsen EO, Grunnet M, et al. Augmentation of cognitive function by NS9283, a stoichiometry-dependent positive allosteric modulator of α2- and α4–containing nicotinic acetylcholine receptors. Br J Pharmacol. 2012 Sep;167(1):164-82. | [17] Millan, M. Agid, Brüne, M., et al. Cognitive dysfunction in psychiatric disorders: characteristics, causes and the quest for improved therapy. Nature reviews Drug discovery, 2012 11(2), 141-168. | [18] Leucht S, Heres S. Epidemiology, clinical consequences, and psychosocial treatment of nonadherence in schizophrenia. J Clin Psychiatry. 2006;67 Suppl 5:3-8. | [19] Thieda P, Beard S, Richter A, Kane J. An economic review of compliance with medication tehraepy in the treatment of schizophrenia. Psychiatr Serv. 2003;54(4):508-516. | [20] Scher-Svanum H, Faries DE, Zhu B, Ernst FR, Swartz MS, Swanson JW. Medication adherence and long-term functional outcomes in the treatment of schizophrenia in usual care. J Clin Psychiatry. 2006;67(3):453-460. | [21] Hayes TL, Larimer N, Adami A, Kaye JA. Medication adherence in healthy elders: small cognitive changes make a big difference. J Aging Health. 2009 Jun;21(4):567-80. | [22] Yee JL, Hasson NK, Schreiber DH. Drug-related emergency department visits in an elderly veteran population. Ann Pharmacother. 2005;39(12):1990-1995. | [23] Kampman O, Lehtinen K. Compliance in psychoses. Acta Psychiatrica Scandinavica. 1999 Sep 100(3):1677-175. | [24] Keith SJ, Kane JM. Partial compliance and patient consequences in schizophrenia: our patients can do better. Journal of Clinical Psychiatry. 2003;64:1308-1315. | [25] Campbell NL, Boustani MA, Skopelja EN, Gao S, Unverzagt FW, Murray MD. Medication adherence in older adults with cognitive impairment: a systematic evidence-based review. Am J Geriatr Pharmacother. 2012 Jun;10(3):165-77. | [26] Hayes TL, Larimer N, Adami A, Kaye JA. Medication adherence in health elders: small cognitive changes make a big difference. J Aging Health. 2009 June;21(4):567-80. | [27] Lehman AF, Lieberman JA, Dixon LB, et al. Practice Guideline for the Treatment of Patients with Schizophrenia. Second Edition. Am J Psychiatry. 2004 Feb;161(2 Suppl):1-56. | [28] Burton SC. Strategies for improving adherence to second-generation antipsychotics in patients with schizophrenia by increasing ease of use. J Psychiatr Pract. 2005;11(6):369-378. | [29] Llorca PM. Partial compliance in schizophrenia and the impact on patient outcomes. Psychiatry Res. 2008 Nov 30;161(2):235-47. | [30] Robinson DG, Woerner MG, Alvir JM, Bilder RM, Hinrichsen GA, Lieberman JA. Predictors of medication discontinuation by patients with first-episode schizophrenia and schizoaffective disorder. Schizophr Res. 2002 Oct 1;57(2-3):209-19 | [31] Herrmann N, Chau SA, Kircanski I, Lanctot KL. Current and emerging drug treatment options for Alzheimer's disease: a systematic review. Drugs. 2011 Oct 22;71(15):2031-65. | [32] Alzheimer's Association. 2011 Alzheimer's disease: facts and figures. Alzheiers Dement. 2011 Mar;7(2):208-44. | [33] Yaari R, Corey-Bloom J. Alzheimer's disease. Semin Neurol. 2007 Feb; 27(1):32-41. | [34] Cappell J, Herrmann N, Cornish S, et al. The pharmacoeconomics of cognitive enhancers in moderate to severe Alzheimer's disease. CNS Drugs. 2010 Nov;24(11):909-27. | [35] Meyer, J.S.; Quenzer, L.F. (2005). Psychopharmacology: Drugs, The Brain, and Behavior. Sunderland, MA: Sinauer Associates. ISBN 0878935347 | [36] Stahl, S. M. (2003). Describing an atypical antipsychotic: receptor binding and its role in pathophysiology. Prim Care Companion J Clin Psychiatry, 5(S3): 9-13. | [37] Stahl S. Schizophrenia: Building Awareness—Advancing Understanding. American Psychiatric Association Annual Meeting. May 14 - 18, 2011. Honolulu, Hawaii. | [38] FreedmanR. Schizophrenia. NEnglJMed2003; 349: 1738–1749 | [39] Noel JM. ASHP therapeutic position statement on the use of second-generation antipsychotic medications in the treatment of adults with psychotic disorders. Am J Health Syst Pharm 2007; 64(8): 863-76 | [40] NIMH Psychoactive Drug Screening Program http://pdsp.med.unc.edu/pdsp.php Accessed October 5, 2013 | [41] Schmidt AW, Lebel LA, Howard HR, Zorn SH (2001), Ziprasidone: a novel antipsychotic agent with a unique human receptor binding profile. Eur J Pharmacol 425(3): 197 | [42] Lamoure J, Psychopharmacology "Boot Camp" Essentials Study Guide Review: 304 pages ISBN 9781300958154 | [43] Abi-Dargham A Laruelle M. Mechanisms of action of second-generation antipsychotic drugs in schizophrenia: insights from brain imaging studies. Eur. Psychiatry. 2005 Jan; 20 (1): 15-27. | [44] Iyer, S., Banks, N., & Roy, M. A. (2013). Qualitative study of experiences with and perceptions regarding long-acting injectable antipsychotics: part I—patient perspectives. Can J Psychiatry, 58(5 Suppl 1), 14S-22S. | [45] Iyer, S., Banks, N., Roy, M. A., Tibbo, P., Williams, R., Manchanda, R., ... & Malla, A. (2013). A Qualitative Study of Experiences With and Perceptions Regarding Long-Acting Injectable Antipsychotics: Part II-Physician Perspectives. Canadian journal of psychiatry. Revue canadienne de psychiatrie, 58(5 Suppl 1), 23S-9S. | [46] Lamoure J., Stovel J., Piamonte M., et al. The Collaborative Patient/Person-Centric Care Model (CPCCM) Introducing a new paradigm in patient care involving an evidence-informed approach. Canadian Healthcare Network. EPub March 7, 2011. http://www.canadianhealthcarenetwork.ca/ | [47] Macqueen G, Campbell S, McEwen B, et al: Course of Illness, Hippocampal Function, and Hippocampal Volume in Major Depression. PNAS 2003; 100(3): 1387–1392 | [48] Rudnick A, Lamoure J., Chapter 6.2- Person Centered Approaches to Psychopharmacology for Persons with Serious Mental Illnesses: Rudnick, A. & Roe, D. (eds). Serious Mental Illness: Patient-Centered Approaches, Oxon, UK:Radcliffe Publishing Ltd., 2011. ISBN9781846193064