



The cognitive footprint of medication: A review of cognitive assessments in clinical trials

Charlotte R. Stoner PhD^{1,2} | Martin Knapp PhD³ | Jeroen Luyten PhD⁴ |
Claryn Kung PhD⁵ | Marcus Richards PhD⁶ | Raj Long MSc⁷ |
Martin Rossor PhD^{1,8}

¹Department of Neurodegenerative Diseases, Queen Square Institute of Neurology, UCL, London, UK

²Research Department of Clinical, Educational and Health Psychology, UCL, London, UK

³Personal Social Services Research Unit, London School of Economics and Political Science, London, UK

⁴Department of Public Health and Primary Care, KU Leuven Leuven Institute for Healthcare Policy, Leuven, Belgium

⁵Monash Business School, Centre for Health Economics, Monash University, Clayton, Vic., Australia

⁶Medical Research Council (MRC) Unit for Lifelong Health and Ageing at UCL, Institute of Cardiovascular Science, UCL, London, UK

⁷Bill and Melinda Gates Foundation, London, UK

⁸National Office of the Director for Dementia Research, National Institute for Health Research, UCL, London, UK

Correspondence

Charlotte R. Stoner, Research Department of Clinical, Educational and Health Psychology, UCL, 1-19 Torrington Place, London, UK.
Email: c.stoner@ucl.ac.uk

Abstract

What is known and objective: Polypharmacy is common, and many medications have cognitive side effects. Such effects can be transient and subside when the drug in question is discontinued or can be long-lasting with effects present for years afterwards. Although formal assessment of cognition is feasible and often undertaken in neuropsychiatric trials, these effects are usually neglected in the evaluation of any non-neuropsychiatric health intervention. Medication effects can be assessed within a cognitive footprint framework, to account for the magnitude and the duration of cognitive side effects, with some likely to have a greater and more lasting effect than others.

Comment: Adverse event reporting suggests that many medications may be indirectly associated with cognitive effects, for example due to headaches, somnolence and 'dizziness'; however, inferring causation from adverse event reporting can be problematic. In order to better understand the impact of investigational drug and concomitant medications effect on cognition, it would be essential to ensure cognition is prioritized in drug development evaluation. It is suggested that simple instruments that can be easily incorporated into existing trial designs are used to assess the cognitive footprint of medication.

What is new and conclusion: We present an overview of existing measures of cognition that can be integrated into drug trials in order to provide a cognitive footprint. Like quality of life testing, such tests should be administered as a standard throughout the key assessment stages of the design of the trial to ensure that any effects on this equally important outcome are also documented. Furthermore, employing routine cognition testing may also enable researchers to identify unanticipated beneficial and non-beneficial effects on cognition. Provision of such a cognitive footprint profile of drugs may provide the necessary evidence to enable decision-makers to make informed decisions on risk-benefit analysis that can subsequently make trade-offs between different drug regimens.

KEYWORDS

clinical trials, dizziness, polypharmacy, psychometric, somnolence

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1 | WHAT IS KNOWN AND OBJECTIVE

Many medications are associated with significant cognitive effects; these cognitive effects are often under-reported, rarely measured in Phase III trials and consequently rarely considered in doctors' and patients' choices between different drug regimens. This neglect of cognition not only hinders informed decision-making but it also misses an important opportunity not only to identify negative effects but also to identify whether medications have a positive effect where cognition is not the primary outcome of interest. Cognitive effect can be on target beneficial effects, for example anticholinesterase inhibitors prescribed for people with Alzheimer's disease,¹ or off-target negative effect such as neurodevelopmental delay in offspring following sodium valproate use by pregnant women.² In addition, medications are commonly prescribed, with 18.6 items prescribed per head in England in 2015.³ This number increases in those over the age of 65 years. Polypharmacy (5-8 prescribed medications) and excessive polypharmacy (≥ 9 prescribed medications) can be particularly problematic for older adults, with both associated with poorer cognitive ability.⁴

Medications can have direct effects on cognition; for example, anticholinergic burden in geriatric inpatients is independently associated with cognitive impairment.⁵ However, medication can also have indirect consequences for cognition, with dizziness, headaches, somnolence and fatigue all having the potential to impair cognitive function. Headaches, a commonly reported side effect of medication,⁶ are associated with abnormalities in memory, attention and information processing speed.⁷

Medications can exert a cognitive effect at any time across the lifespan, for example the effect of sodium valproate *in utero*, and the association of an increased risk for cerebral palsy and neurodevelopmental delay with postnatal steroid therapy in early infancy.⁸ In children, some noradrenaline reuptake inhibitors (NRI) are effective for cognitive and behavioural symptoms of attention deficit hyperactivity disorder (ADHD), but are associated with potential cognitive adverse events such as somnolence, dizziness and fatigue.⁹ In adulthood, chemotherapy is associated with self-reported cognitive impairment, sometimes called 'chemobrain' or 'chemofog',¹⁰ and fatigue can be a common adverse event.¹¹ Triptans including zolmitriptan are increasingly prescribed for migraines, but the benefit of headache abortion should be evaluated in the context of an increased risk of cognitive adverse events including dizziness and somnolence.¹² For older adults, antimuscarinics can be prescribed to treat urge incontinence or nocturia but are also associated with an increased risk of cognitive decline.¹³

Cognitive side effects can be long-lasting and have serious implications for health and well-being. For example, 'chemobrain' has been reported to last up to 20 years following adjuvant chemotherapy,¹⁴ and some medications appear to increase the risk of later dementia. In particular, medications with an anticholinergic burden score of three are associated with an increased risk of a dementia diagnosis 15-20 years later (RR 1.11; 95% CI 1.08 to 1.14).⁵ Further, there is often disparity between clinical and statistical significance

for adverse effects and the current configuration of clinical trials limits the degree to which both clinical significance and delayed adverse events can be accurately captured. This is particularly relevant for very rare cognitive effects classed by the British National Formulary as 1 in 10 000 to 1 in 1000. Such effects are unlikely to be captured in Phase III trials but may be captured in Phase IV postmarketing surveillance studies. However, the reporting of these cognitive effects can be reliant on voluntary reporting schemes such as the Yellow Card Scheme.¹⁵

However, the majority of cognitive effects are transient, for example a drug-induced headache¹⁶ or adverse events such as somnolence or dizziness. These effects will generally subside after a medication is discontinued but, while being prescribed, any benefit to the primary condition should be evaluated in the context of this potential adverse effect. Furthermore, although the effects of medication may be transient, when they occur in large groups of people they nonetheless generate a large aggregate burden, both in terms of health as in indirect effects on productivity, disturbed daily activities, etc. Moreover, although the cognitive effects can be transient, their long-term consequences in terms of human capital acquisition may nevertheless be permanent, such as reduced educational opportunities or career interruptions and ultimately societal impact.

We argue that in addition to the usual outcomes on which medications are typically tested, they should also be evaluated in terms of their specific cognitive impact. This approach to medication effects can be conceptualized within a 'cognitive footprint' framework that assesses not only the size of an effect but also the duration.¹⁷ Although cognition is more complex to evaluate than usual outcomes, there are reliable and meaningful resources available to researchers aiming to do so. In this article, we provide an overview of available measures that can be used to assess the cognitive effects of drugs. We first discuss the various available cognition measures in the neuropsychiatry and paediatrics domain, and then, we assess the usefulness of adverse events reporting.

2 | COMMENT

2.1 | Measuring cognition

The standardized measurement of cognition in CTIMPS is usually within a deficit paradigm, with the focus on measures of cognitive impairment. Thus, the standardized measurement of cognition is usually only employed in samples where there is pre-existing cognitive impairment, such as in dementia research, and where cognitive impairment is of importance from a developmental perspective, as in childhood studies.¹⁸ Outside of these populations, cognition is usually not measured as standard in clinical trials. This stands in contrast to health-related quality of life (HRQoL), which has gained much traction in recent decades and is now almost universally measured in health research.¹⁹ With the development of health technology assessment and cost-effectiveness analysis based on health outcome measures such as quality- or disability-adjusted life years



as currencies to measure the health gains of drugs, surveys that monitor the HRQoL are routinely taken from patients. Standard surveys such as the EuroQoL or SF-6D predominantly focus on physical health impacts and incorporate only very narrow mental outcomes. For instance, the EuroQoL assesses impacts on anxiety and depression and the SF-6D assesses vitality and whether someone feels downhearted. But cognitive effects are excluded and hence not considered part of HRQoL. This exclusion not only has implications for the assessment of the effectiveness of drugs but it also influences resource allocation decisions. Patient access to medical products is optimal when the right patient receives the right medication at the right time in-line with the WHO Sustainable Development Goals. Moreover, the neglect of cognition misses an important opportunity to identify negative effects but also to identify whether medications have a positive effect where cognition is not the primary outcome of interest.

2.1.1 | Neuropsychiatric cognition measures

Some of the more commonly measures are discussed below, but more comprehensive lists were beyond the scope of the current manuscript and are covered by other reviews.²⁰

The most well-known cognition measure for people with Alzheimer's disease or other dementias is the Mini-Mental State Examination (MMSE).²¹ It is widely used and has been translated into at least 15 other languages.²² However, the MMSE²³ is less able to accurately capture milder forms of cognitive impairment such as those related to age.²⁴ It also has low sensitivity when used among individuals with general neurological and psychiatric conditions.²⁵ In practice, the MMSE is also heavily weighted towards literacy skills, with significant correlations noted to be higher for literacy level than other demographic variables.²⁶

Other measures used to screen for cognitive impairment include the Montreal Cognitive Assessment (MoCA),²⁷ the Alzheimer's Disease Assessment Scale Cognitive Subscale (ADAS-Cog),²⁸ the Addenbrooke's Cognitive Examination (ACE-III),²⁹ the Cambridge Cognitive Examination (CAMCOG),³⁰ the Saint Louis University Mental State Examination (SLUMS),³¹ the General Practitioner Assessment of Cognition (GPCOG),³² the Mini-Cog³³ and the Abbreviated Mental Test (AMT).³⁴ Of these measures, the MoCA has been increasingly used, potentially due to its increased sensitivity for mild cognitive impairment, compared with the MMSE.²⁷ Furthermore, the MoCA has also been applied in a range of populations including cancer,³⁵ diabetes,³⁶ famine³⁷ and epilepsy.³⁸ However, most of the dementia-specific screening tools are subject to limitations, including ceiling effects when used in other populations. For example, it has been suggested that the ADAS-Cog relies overly on memory testing³⁹ and the reliability of the AMT has been questioned with 80% of junior doctors in one study failing to use the test accurately.⁴⁰

Cognition testing is used frequently for people with a diagnosis of schizophrenia. The Brief Assessment of Cognition in Schizophrenia

(BACS) is a composite measure of existing cognitive tests designed to assess impairment in verbal memory, working memory, motor speed, verbal fluency, attention and speed of information processing and executive function.⁴¹ The BACS was specifically developed for people with schizophrenia with a focus on the aspects of cognition found to most be impaired in this population. While it has been validated in some other populations such as older adults with bipolar disorder,⁴² it may hold less validity for clinical populations. The Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) was also developed to assess the clinical effectiveness of medication, cognitive remediation among adults with schizophrenia and to provide a reference point for non-intervention studies of schizophrenia.⁴³ Like the BACS, the MCCB is focused primarily on specific deficits associated with schizophrenia including social cognition. An assessment of the relevance of the MCCB for bipolar populations concluded that the deficits measured by the MCCB were weighted towards more severe impairment than was needed for a bipolar population; it was thus suggested that different sub-tests were more appropriate.⁴⁴

Other neuropsychiatric populations for which cognition testing is becoming increasingly common are those of major depressive disorder (MDD) and bipolar disorder. However, this field is limited due to the subjective nature of assessments used and a bias towards negative cognitive schemas.⁴⁵ This limitation is apparent in analyses of the Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire (CPFQ), in which no correlation was found between self-reported cognitive difficulties on the CPFQ and a clinician-administered instrument of cognition.⁴⁶

2.1.2 | Paediatric cognition measures

Clinical paediatric cognition measures are employed for diagnosis, screening, research, programme evaluation and intervention planning.¹⁸ The measures are often set within classic psychological frameworks such as Piaget's four stages of cognitive development, namely sensorimotor, preoperational, concrete operational and formal operational.⁴⁷ Some measures that are not appropriate for an adult population, for example the Bayley Scales of Infant and Toddler Development—Third Edition (BSID-III),⁴⁸ are not discussed here.

Measures of attention and executive functioning may provide valuable indications of impairment secondary to drug effects. Conners' Continuous Performance Task-II (CPT II) is a measure of sustained and selective attention⁴⁹ as is the Trail Making Test (TMT).⁵⁰ In a review, both measures were determined to be approaching 'well-established' criteria, with favourable psychometric properties in samples of children with attention deficit hyperactivity disorder (ADHD).⁵¹ However, reviewers noted that the test-retest reliability of the CPT II was variable ranging from 0.5 to 0.92 and that both measures are used within a diagnostic framework, where the aim is to distinguish non-impaired controls from individuals with neurological or learning impairments. Moreover, adult studies of the

CPT II are mainly limited to adults with a traumatic brain injury,⁵² limiting its usefulness outside of these settings. The TMT has also been used in adult settings (18-89 years of age), with normative data stratified by age group and education.⁵³ Results suggest that age accounts for more variance on both Trails A and B (34% and 38%), while education accounts for less variance (3% and 6%) allowing for a comparison of cognitive function while controlling for varying ages and education. As such, the TMT may be an appropriate tool to measure the cognitive effects of medications for both paediatric and healthy populations.

2.1.3 | Adverse event reporting

Outside of neurological and psychiatric trials, cognitive measurement and consequently cognitive assessment are rarely performed. However, one way to evaluate potential cognitive effects of medication is to examine adverse events. Safety reporting is mandatory in trials of medication and is classified as adverse event/reaction (AE/AR), serious adverse event/reaction (SAE/SAR) or a suspected unexpected serious adverse reaction (SUSAR). All clinical trials of an investigational medicinal product (CTIMPs) are required to collect information regarded as critical to the evaluation of the safety of a medicinal product and report this information to a study sponsor. However, only SAEs and SUSARs need to be reported to the sponsor and in some cases the relevant Research Ethics Committee (REC).⁵⁴

Current MEDRA classification system may enable cognitive signals to emerge but determining what constitutes a cognitive AE can be problematic, with dizziness, insomnia, somnolence, headaches and fatigue all having the ability to impair cognition. Data on medication-induced cognitive adverse events are sparse and are usually limited to specific reactions. However, there are several problems. First, what data are available suggest that cognitive adverse events are under-reported and under-researched. For example, headache is a frequently reported adverse event implicated in a range of medications,⁵⁵ and the use of opioid analgesics can increase incidence of somnolence and dizziness.⁵⁶ Second, the impact of these events can be difficult to determine, with statistical testing used variably. In some cases, only percentages of participants reporting adverse events in both the active and the control groups are described, and no formal analysis is undertaken of the effects size. Third, drowsiness, nausea, fatigue, headache and insomnia are often reported as a nocebo effect,⁵⁷ which can confound such results.⁵⁸ Fourth, observable outcomes related to these events are lacking and the relationship between multiple adverse cognitive effects is likely to be complicated. This relationship may consist of trade-offs where, for example, a positive effect on cognition from reducing pain may also have a negative effect on cognition by increasing drowsiness or sedation.⁵⁹ However, the use of AEs as a cognitive surrogate is inadequate and so cognitive measures are needed.

2.2 | Scalable measures of cognition in trials

Given the limitations associated with AE reporting, measures of attention may give an indication of overall cognitive impairment and enhancement perspective, but are also sensitive to specific cognitive domains such as executive function and processing speed. The Deary-Liewald Reaction Time task (DLRT) is a freely available measure of reaction and choice reaction time. Preliminary psychometric properties of the DLRT are promising, with excellent internal consistency and observed, expected correlations with age. However, it should be noted that the choice reaction time section of the test had more robust psychometric properties.⁶⁰ Furthermore, more empirical investigations of the DLRT are needed to further determine its ability to detect cognitive change.

The Stroop test measures the executive requirement to screen out distracting information, for example the challenge of calling out the colour in which a word is printed when this is incongruent with what the word says (eg blue written in a red font).⁶¹ Since its inception in 1935, numerous researchers have published studies and reviews exploring the effect in a range of populations including adolescents with ADHD,⁶² young adults, older adults and people with Alzheimer's Disease.⁶³ Within the latter study, the Stroop test was sensitive to age effects with authors attributing the decline in performance to the loss of inhibitory processing. As an indication of intraindividual cognitive fluctuation, or the degree to which cognition fluctuates from baseline to follow up within persons, the Stroop may be a useful tool for the cognitive footprint of a medication. Furthermore, the Stroop test can be visualized as on a spectrum, with no established criteria separating clinically impaired from unimpaired. It may, therefore, also be appropriate to assess sub-clinical levels of impairment or enhancement across a range of medications and may be a means of evaluating the observable impact of side effects such as somnolence or headaches on cognition.

In terms of more detailed assessment, Cambridge Cognition has developed two computerized systems to address the lack of observable outcomes associated with drug-induced cognitive impairment. Named the Clinical Trial Information System-Profile (CTIS-Profile) and Clinical Trial Information System-Profile 2+ (CTIS-Profile 2+), the systems incorporate measures of processing speed, sustained attention, working memory, visual episodic memory and executive function to determine whether medications are implicated in observable cognitive impairment. The CTIS measures are rigorous and primarily designed for use in CTIMPs. However, associated costs and time to complete may limit use outside of formal trials or across disciplines.

3 | WHAT IS NEW AND CONCLUSION

Cognition is a fundamental aspect of life, allowing individuals to function fully as individuals and as members of a society. The neglect of cognitive testing as routine may be due to a pervading viewpoint that cognition is only relevant for populations such as those with

Alzheimer's disease and evidenced by the abundance of cognition measures developed for these populations. The cognitive footprint is a theoretical framework in which cognition is viewed as a vital outcome across the lifespan that significantly influences the health, social and economic state of individuals and that deserves to be included in any drug, health or broader policy evaluation. Furthermore, cognition is conceptualized as a broad spectrum of abilities, with factors at different ages exerting transient or long-lasting effects on function. Such factors may enhance or impair cognition and summate in determining the cognitive capabilities of individuals or societies.

However, as reviewed here, measures of cognition used in trials are measures of cognitive impairment developed from a deficit standpoint, with ceiling effects evident for clinically non-impaired populations. This misses an important opportunity to identify the cognitive effects of a range of medications in trials beyond those with neuropsychiatric outcomes. Thus, current measures of cognition are not suitable for assessing different cognitive footprints. Further, each measure identified would need to be subject to a psychometric appraisal to ensure it remains a valid and reliable tool to measure cognitive change in each population in which it is employed.

With regard to assessing the cognitive footprint of medications, adverse event reporting suggests that many drugs have cognitive adverse effects that may be mediated through non-specific symptoms such as dizziness, somnolence and headaches. However, using adverse event reporting to ascertain cognitive effects is problematic, and cognitive symptoms are usually not given weight, with medications implicated described as well-tolerated.⁶⁴ While the acceptability of these symptoms is likely to be very variable, with patients able to tolerate differing levels of cognitive symptoms, the importance of these effects for quality of life of activities of daily living can be underestimated. Furthermore, there have been no formal examinations of the association between these adverse events and standardized measures of cognition. As such the degree to which, for example, medication-induced somnolence affects cognition as assessed using outcome measurement is currently unknown. The physical examination in trials is conducted regularly and to a standard format and would benefit from the addition of a cognitive module. We suggest that measures of cognition such as the Stroop test or the DLRT may be an appropriate means of assessing cognitive effects of medications. Such tests are often easy to administer, with short completion times, minimal training required and they can be easily utilized outside the clinical context. Compared with systems such as CTIS, these tests are also in the public domain, which is in-line with Open Science principles and allows for their uptake across disciplines with minimal associated costs. Incorporating these tests as standard in both clinical practice and research will ensure that the cognitive impact of a wide range of medications can be formally examined, assessed and actioned where required at the individual and societal level.

Like quality of life, cognition is a fundamental component of health and well-being. However, as an outcome, cognition is overlooked within current clinical trials where this is not a formal outcome. Adverse event reporting suggests that medications are often

implicated in a range of cognitive adverse effects but the association between these effects and formal measures of cognition is yet to be explored. It is suggested that cognition testing should be incorporated into a wide range of trials as standard, to ensure that both negative effects but also off-target beneficial effects to cognition can be evaluated. As per the cognitive footprint policy, this will ensure that cognition is prioritized within research but also that it is given due attention more downstream in policy-making and resource allocation. This will help to ensure cognition is given every consideration by both clinical trialists and regulators.

ORCID

Charlotte R. Stoner  <https://orcid.org/0000-0002-1536-4347>

Martin Knapp  <https://orcid.org/0000-0003-1427-0215>

Jeroen Luyten  <https://orcid.org/0000-0001-6398-4025>

Claryn Kung  <http://orcid.org/0000-0003-2863-9423>

Marcus Richards  <https://orcid.org/0000-0001-9191-2192>

Martin Rossor  <https://orcid.org/0000-0001-8215-3120>

REFERENCES

1. Wang CH, Wang LS, Zhu N. Cholinesterase inhibitors and non-steroidal anti-inflammatory drugs as Alzheimer's disease therapies: an updated umbrella review of systematic reviews and meta-analyses. *Eur Rev Med Pharmacol Sci*. 2016;20(22):4801-4817.
2. Bromley R, Weston J, Adab N, et al. Treatment for epilepsy in pregnancy: neurodevelopmental outcomes in the child. *Cochrane Database of Systematic Reviews*, 2014. <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD010236.pub2/abstract>.
3. Baker C. Medicine statistics: GP prescribing by constituency. 2015;2016.
4. Rawle MJ, Cooper R, Kuh D, Richards M. Associations between polypharmacy and cognitive and physical capability: a British Birth Cohort Study. *J Am Geriatr Soc*. 2018;66(5):916-923.
5. Coupland CAC, Hill T, Dening T, Morriss R, Moore M, Hippisley-Cox J. Anticholinergic drug exposure and the risk of dementia. *JAMA Intern Med*. 2019;179(8):1084.
6. Bagdy GRP, Kecskeméti V, Chase D, Juhász G. Headache-type adverse effects of NO donors: vasodilation and beyond. *Br J Pharmacol*. 2010;160(1):20-35.
7. de Araújo CM, Barbosa IG, Lemos SMA, Domingues RB, Teixeira AL. Cognitive impairment in migraine: a systematic review. *Dement Neuropsychol*. 2012;6(2):74-79.
8. Barrington KJ. The adverse neuro-developmental effects of post-natal steroids in the preterm infant: a systematic review of RCTs. *BMC Pediatr*. 2001;6:1.
9. Cheng JYW, Chen RYL, Ko JSN, Ng EML. Efficacy and safety of atomoxetine for attention-deficit/hyperactivity disorder in children and adolescents—meta-analysis and meta-regression analysis. *Psychopharmacology*. 2007;194(2):197-209.
10. Hutchinson AD, Hosking JR, Kichenadasse G, Mattiske JK, Wilson C. Objective and subjective cognitive impairment following chemotherapy for cancer: a systematic review. *Cancer Treat Rev*. 2012;38(7):926-934.
11. Abdel-Rahman O, Fouad M. Risk of fatigue and hepatic and metabolic toxicities in patients with solid tumors treated with everolimus: a meta-analysis. *Future Oncol*. 2015;11(1):79-90.
12. Chen LC, Ashcroft DM. Meta-analysis of the efficacy and safety of zolmitriptan in the acute treatment of migraine. *Headache*. 2008;48(2):236-247.

13. Moga DC, Abner EL, Wu Q, Jicha GA. Bladder antimuscarinics and cognitive decline in elderly patients. *Alzheimer's Dement.* 2017;3(1):139-148.
14. Koppelmans V, Breteler MMB, Boogerd W, Seynaeve C, Gundy C, Schagen SB. Neuropsychological performance in survivors of breast cancer more than 20 years after adjuvant chemotherapy. *J Clin Oncol.* 2012;30(10):1080-1086.
15. National Institute for Health and Care Excellence (NICE). Adverse Reactions to Drugs. 2020. <https://bnf.nice.org.uk/guidance/adverse-reactions-to-drugs.html>. Accessed 9 March, 2020.
16. Tfelt-Hansen PC, Tfelt-Hansen J. Nitroglycerin headache and Nitroglycerin-induced primary headaches from 1846 and onwards: a historical overview and update. *Headache.* 2009;49:445-456.
17. Rossor M, Knapp M. Can we model a cognitive footprint of interventions and policies to help to meet the global challenge of dementia? *Lancet.* 2015;386(9997):1008-1010.
18. Ellingsen KM. Standardized assessment of cognitive development: instruments and issues. In: Garro A, ed. *Early Childhood Assessment in School and Clinical Child Psychology.* New York, NY: Springer Science+Business Media; 2016:25-49.
19. Addington-Hall J, Kalra L. Who should measure quality of life? *BMJ.* 2001;322(7299):1417-1420.
20. Cullen B, O'Neill B, Evans JJ, Coen RF, Lawlor BA. A review of screening tests for cognitive impairment. *J Neurol Neurosurg Psychiatry.* 2007;78(8):790-799.
21. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res.* 1975;12(3):189-198.
22. Steis MR, Schrauf RW. A review of translations and adaptations of the Mini-Mental State Examination in Languages other than English and Spanish. *Res Gerontol Nurs.* 2009;2(3):214-224.
23. Crum RM, Anthony JC, Bassett SS, Folstein MF. Population-based norms for the mini-mental state examination by age and educational level. *JAMA.* 1993;269(18):2386-2391.
24. Gluhm S, Goldstein J, Loc K, Colt A, Van Liew C, Corey-Bloom J. Cognitive performance on the mini-mental state examination and the montreal cognitive assessment across the healthy adult lifespan. *Cogn Behav Neurol.* 2013;26(1):1-5.
25. Tombaugh TN, McIntyre NJ. The mini-mental state examination: a comprehensive review. *J Am Geriatr Soc.* 1992;40:922-935.
26. Weiss BD, Reed R, Kligman EW, Abyad A. Literacy and performance on the mini-mental state examination. *J Am Geriatr Soc.* 1995;43(7):807-810.
27. Nasreddine ZS, Phillips NA, Bédirian V, et al. The montreal cognitive assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc.* 2005;53(4):695-699.
28. Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. *Am J Psychiatry.* 1984;141(11):1356-1364.
29. Mioshi E, Dawson K, Mitchell J, Arnold R, Hodges JR. The Addenbrooke's Cognitive Examination Revised (ACE-R): a brief cognitive test battery for dementia screening. *Int J Geriatr Psychiatry.* 2006;21:1078-1085.
30. Roth M, Tym E, Mountjoy CQ, et al. CAMDEX: a standardised instrument for the diagnosis of mental disorder in the elderly with special reference to the early detection of dementia. *Br J Psychiatry.* 1986;149:698-709.
31. Tariq SH, Tumsa N, Chibnall JT, Perry MH, Morley JE. Comparison of the Saint Louis University mental status examination and the mini-mental state examination for detecting dementia and mild neurocognitive disorder—A Pilot Study. *Am J Geriatr Psychiatry.* 2006;14(11):900-910.
32. Brodaty H, Pond D, Kemp NM, et al. The GPCOG: a new screening test for dementia designed for general practice. *J Am Geriatr Soc.* 2002;50(3):530-534.
33. Borson S, Scanlan J, Brush M, Vitaliano P, Dokmak A. The Mini-Cog: a cognitive 'vital signs' measure for dementia severity in multi-lingual elderly. *Int J Geriatr Psychiatry.* 2000;15:1021-1027.
34. Hodkinson HM. Evaluation of a mental test score for assessment of mental impairment in the elderly. *Age Ageing.* 2012;41(suppl_3):iii35-iii40.
35. Libert Y, Dubruille S, Borghgraef C, et al. Vulnerabilities in older patients when cancer treatment is initiated: does a cognitive impairment impact the two-year survival? *PLoS ONE.* 2016;11(8):e0159734.
36. Zheng T, Qin L, Chen B, et al. Association of plasma DPP4 activity with mild cognitive impairment in elderly patients with type 2 diabetes: results from the GDMD Study in China. *Diabetes Care.* 2016;39(9):1594-1601.
37. Wang C, An Y, Yu H, et al. Association between exposure to the Chinese famine in different stages of early life and decline in cognitive functioning in adulthood. *Front Behav Neurosci.* 2016;10:146.
38. Palanisamy A, Rajendran NN, Narmadha MP, Ganesvaran RA. Comparative assessment of Montreal Cognitive Assessment (MOCA) and Minimental State Examination (MMSE) in apolipoprotein E (APOE) $\epsilon 4$ allele carriers in epilepsy. *Int J Epilepsy.* 2016;3(1):7-11.
39. Wesnes KA, Harrison JE. The evaluation of cognitive function in the dementias: methodological and regulatory considerations. *Dialogues Clin Neurosci.* 2003;5(1):77-88.
40. Jitapunkul S, Pillay I, Ebrahim S. The abbreviated mental test: its use and validity. *Age Ageing.* 1991;20(5):332-336.
41. Keefe RSE, Goldberg TE, Harvey PD, Gold JM, Poe MP, Coughenour L. The brief assessment of cognition in schizophrenia: reliability, sensitivity, and comparison with a standard neurocognitive battery. *Schizophr Res.* 2004;68(2):283-297.
42. Cholet J, Sauvaget A, Vanelle JM, et al. Using the Brief Assessment of Cognition in Schizophrenia (BACS) to assess cognitive impairment in older patients with schizophrenia and bipolar disorder. *Bipolar Disord.* 2014;16(3):326-336.
43. Neuchterlein KH, Green MF, Kern RS, et al. The MATRICS consensus cognitive battery, part 1: test selection, reliability, and validity. *Am J Psychiatry.* 2008;165:203-213.
44. Yatham LN, Torres IJ, Malhi GS, et al. The International Society for Bipolar Disorders-Battery for Assessment of Neurocognition (ISBD-BANC). *Bipolar Disord.* 2010;12(4):351-363.
45. Lam RW, Kennedy SH, McIntyre RS, Khullar A. Cognitive dysfunction in major depressive disorder: effects on psychosocial functioning and implications for treatment. *Can J Psychiatry.* 2014;59(12):649-654.
46. Svendsen AM, Kessing LV, Munkholm K, Vinberg M, Miskowiak KW. Is there an association between subjective and objective measures of cognitive function in patients with affective disorders? *Nord J Psychiatry.* 2012;66(4):248-253.
47. Piaget J. *The Origins of Intelligence in Children.* New York, NY: International Universities Press; 1952.
48. Bayley N. *Bayley Scales of Infant and Toddler Development III (screening test).* San Antonio, TX: Pearson; 2005.
49. Conners C, Staff M. *Conners' Continuous Performance Test II: Computer Program for Windows Technical Guide and Software Manual.* North Tonawanda, NY: Multi-Health Systems. 2000.
50. Reitan RM, Wolfson D. *The Halstead-Reitan Neuropsychological Test Battery: Theory and Clinical Interpretation,* 2nd edn. Tuscon, AZ: Neuropsychological Press; 1993.
51. Campbell JM, Brown RT, Cavanagh SE, Vess SF, Segall MJ. Evidence-based assessment of cognitive functioning in pediatric psychology. *J Pediatr Psychol.* 2008;33(9):999-1014.
52. Ord JS, Boettcher AC, Greve KJ, Bianchini KJ. Detection of malingering in mild traumatic brain injury with the Conners' Continuous Performance Test-II. *J Clin Exp Neuropsychol.* 2010;32(4):380-387.

53. Tombaugh TN. Trail Making Test A and B: Normative data stratified by age and education. *Arch Clin Neuropsychol*. 2004;19(2):203-214.
54. *The Medicines for Human Use (Clinical Trials) Regulations*. London, UK: UK Government; 2004.
55. Ferrari A, Spaccapelo L, Gallesi D, Sternieri E. Focus on headache as an adverse reaction to drugs. *J Headache Pain*. 2009;10(4):235-239.
56. Ohishi A, Chisaki Y, Hira D, Nagasawa K, Terada T. Opioid analgesics increase incidence of somnolence and dizziness as adverse effects of pregabalin: a retrospective study. *J Pharm Health Care Sci*. 2015;1:30.
57. Wells RE, Kaptchuk TJ. To tell the truth, the whole truth, may do patients harm: the problem of the nocebo effect for informed consent. *Am J Bioeth*. 2012;12(3):22-29.
58. Planès S, Villier C, Mallaret M. The nocebo effect of drugs. *Pharmacol Res Perspect*. 2016;4(2):e00208.
59. Dhingra L, Ahmed E, Shin J, Scharaga E, Magun M. Cognitive effects and sedation. *Pain Med*. 2015;16(Suppl 1):S37-S43.
60. Deary IJ, Liewald D, Nissan J. A free, easy-to-use, computer-based simple and four-choice reaction time programme: the Deary-Liewald reaction time task. *Behav Res Methods*. 2011;43(1):258-268.
61. Stroop JR. Studies of interference in serial verbal reactions. *J Exp Psychol*. 1935;18(6):643-662.
62. Homack S, Riccio CA. A meta-analysis of the sensitivity and specificity of the Stroop Color and Word Test with children. *Arch Clin Neuropsychol*. 2004;19(6):725-743.
63. Spieler DH, Balota DA, Faust ME. Stroop performance in healthy younger and older adults and in individuals with dementia of the Alzheimer's type. *J Exp Psychol Hum Percept Perform*. 1996;22(2):461-479.
64. Ryan NM. A review on the efficacy and safety of gabapentin in the treatment of chronic cough. *Expert Opin Pharmacother*. 2015;16(1):135-145.

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