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Cognition assessment in paediatric clinical trials

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As in adults and the elderly, a number of paediatric conditions have a recognised cognitive dysfunction. Studies also demonstrate adverse cognitive effects associated with medicinal products used in paediatric populations. Demonstrating efficacy in treating cognitive dysfunction, or safety and tolerability in minimising adverse cognitive effects is as relevant to paediatric clinical trials as it is to adult populations. Indeed, cognitive assessments may be even more vital in paediatric populations, due to the additional possibility of adverse effects on cognitive development. This requirement to evaluate cognition in children and adolescents, and new legislation for paediatric clinical trials, has created an increased demand for suitable assessment methods.

The terms 'cognition' or 'cognitive function' testing may be used to describe a number of different assessment approaches ranging from patient reported outcomes at the level of spontaneously reported events, through structured interviews, scales and questionnaires, to objective tests. Objective tests may assess general concepts such as intelligence and/or more specific individual cognitive domains and functions such as attention and memory, but all are designed to measure task performance in some way. Traditional neuropsychological assessment has typically involved administration of comprehensive batteries of tests, each assessing different aspects of cognition. Over the past 20 years, a number of computerised tests and test batteries have been developed, specifically designed for use in psychopharmacological research and clinical trials. This is in contrast to classical neuropsychological test batteries, which have primarily been designed as comprehensive, single, diagnostic assessments for an individual. These types of neuropsychological assessment may be used as diagnostic tests in some indications. However, we are concerned here with the measurement of change over time.

The use of cognitive function assessment is now well established in all phases of clinical research for example in both recent draft EMEA dementia guidelines and the NIMH funded MATRICS initiative, recommendations have been out forward for areas of cognition to be assessed in clinical trials, which will be covered in more detail later. Whilst in paediatric clinical trials cognition assessment is common in both studies of epilepsy [1,2] and attention disorders [3]. Cognitive assessments may be employed in several ways: as safety and tolerability outcomes; to generate hypotheses for later studies; for proof of concept before patient studies/larger scale studies; and as efficacy outcomes. A number of crucial requirements for cognitive/neuropsychological test batteries have been identified and these should guide the selection of appropriate assessments for clinical trials use, but issues specific to paediatric assessment such as age appropriate methods and existing profiles of cognitive impairment in each indication, must also be borne in mind.

New European legislation on paediatric medicines came into force on 26 January 2007 [4]. This legislation sets out obligations for the conduct of clinical trails in paediatric populations. The intention of this legislation has been to address problems of inadequate dosage information; and non-availability of therapeutic advances, dose formulations and routes of administration in paediatric populations. The legislation is expected to stimulate research and result in increased numbers of paediatric clinical trials, overseen by the new Paediatric Committee within the EMEA. Thus it is anticipated accessibility, efficacy and safety of medicinal products in paediatric populations will be improved. Consequently, it can also be expected that these pressures will

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create an increased need for cognition assessment in paediatric clinical trials.

Several issues specific to paediatric clinical trials reinforce the need for cognition assessment. A number of the pharmacovigilance considerations outlined in the concept paper on conduct of pharmacovigilance for medicines used by children [5] should be applied to cognition assessment, in particular the specific issue of cognitive development in infants, children and adolescents. This concern makes cognition assessment data crucial to evaluating risk/benefit for any pharmacotherapy intended for paediatric use. Infants, children and adolescents are especially at risk if drugs adversely affect brain development and/or educational progress, and it would be a major concern if efficacious paediatric medicines resulted in premature cognitive decline or retarded cognitive/academic development [6]. Further to this, children may be poor at expressing their symptoms, making spontaneously reported adverse drug events less valuable. Whilst this can be addressed in part by the use of reports from parents/carers or clinicians, objective tests also provide a sound methodology for generating pharmacovigilance data. In addition, concerns to ensure any procedures conducted on children are as non-invasive as possible (particularly minimising blood draws and other painful procedures) focus attention on cognition and other assessment techniques such as fMRI, as possible biomarkers for paediatric research.

A search of the online National Centre for Biotechnology Information ''PubMed'' database retrieved 5089 publications of clinical trials in children and adolescents between 2 and 18 years of age, published between January and August 2007. Of these, 15 reported the use of IQ measures, with the most common being the Wechsler Intelligence Scale for Children (WISC), designed for children/adolescents between 6 and 16 years of age, and the Wechsler Preschool and Primary Scale of Intelligence (WPPSI) designed for children aged 2.5–7.5 years of age. A further 167 reported use of various types of behavioural rating, whilst a greater proportion (276) employed various different cognitive/neuropsychological assessments.

The purpose of the present review will be to highlight the importance of well-validated, objective assessments of cognition in paediatric clinical trials. The importance of objective assessment in addition to patient reported outcomes will be discussed, along with advantages of cognitive/neuropsychological assessment as opposed to IQ testing. Whilst the importance of other aspects of function, and their possible interaction with cognition should not be underestimated, the present review is intended to address issues in cognitive/neuropsychological assessment directly. A great number of ratings designed to assess stress, depression, anxiety, aggression, experience of pain, motor abilities, social function, quality of life, etc. are in use, and each would present a broad review topic in itself.

Comparison of observational and self-reported measures, and objective assessments

Whilst spontaneously reported suspected adverse drug reactions are still the most important source of information for detecting safety issues, children may be poor at expressing symptoms. Chambers and Johnston [7] report that younger children used much more extreme responses in comparison to older children when using likert scales to rate emotional states, whilst other studies looking at clinical assessments indicate both under-reporting of symptoms [8] (self-reported nasal congestion versus objective nasal airway resistance) and over-reporting of symptoms [9] (subjective sleep complaints in children with abdominal pain versus objective sleep measures in comparison to healthy peers). Whilst EMEA groups suggest that the roles of different groups of reporters be considered (e.g. parents), this ignores the possible benefits of objective cognitive assessments, which have already been demonstrated in adult populations, and dissociations have also been seen between subjective and objective measures in adults. Harrison and Wesnes [10] report a number of studies, which demonstrate that dissociations between observational/self-report measures and objective cognitive assessments are an important safety concern in adult clinical trials. For example, data from one study showed that the Bond-Lader Visual Analogue Scales self-rated measure of alertness was less sensitive in discriminating the ability of different doses of physostigmine to reverse impairments to attention induced by scopolamine, than a reaction time measure [11]. In another study, a marked objective impairment of attention was seen in elderly volunteers 48 hours after a final dose of haloperidol, which was not seen in subjective ratings of alertness. This was shortly before the planned discharge from the clinic, thus presenting a clear safety issue [12]. These dissociations may arise for a number of reasons, including a lack of awareness of drug effects, threshold effects, differential sensitivity, or reduced insight caused by drug-induced impairment of cognition. Thus the need for objective assessment of cognition to evaluate safety is clear in adults, and can be considered to be potentially more important in paediatric populations, who may lack the insight and ability to verbalise symptoms of adult participants.

One other important supplementary area of assessment is that of the structured behavioural rating. The most commonly used of these reported in the PubMed search of paediatric clinical trials over the past year was the Child Behavior Checklist (CBCL) [13]. The CBCL is designed for ages 6–18 (CBCL/6–18) (for children too young for the CBCL/6–18, the Child Behavior Checklist/1 1/2–5 (CBCL/1 1/2–5/LDS) may be used instead) and obtains reports from parents, other close relatives, and/or guardians regarding children's competencies and behavioural/emotional problems. Of particular relevance to cognitive function are items assessing 'Attention Problems', with individual questions such as whether the child is 'Inattentive or easily distracted', and 'Can't concentrate, can't pay attention for long'. This type of assessment is useful in being able to gather information on a range of important behaviours from adults who know the child well. Though still open to those potential problems outlined above regarding subjective measures, a further issue with this type of assessment is that it relies on observing the child displaying these behaviours. Therefore, change is unlikely to be measured over short durations of time and this type of assessment could not be meaningfully repeated several times over the course of a day. In addition, the assessment does not attempt to measure specific domains of cognitive function such as memory independently, an issue which will be discussed further below. Therefore, objective assessments may have the advantage of confirming subjective or observational data, or may be more suited to repeated assessment or studies of shorter duration.

A consensus on essential attributes for cognitive/neuropsychological assessment?

The potential benefits of the addition of objective cognitive measures to clinical trials may include more sensitive and appropriate assessment, ability to measure change in smaller populations or over shorter periods of time and better monitoring of treatment safety. However, whilst it is clear that assessments of IQ and cognitive/neuropsychological function are in wide use, there are huge numbers of assessment options available and very little standardisation of assessment approaches, or regulatory guidance with respect to these assessments. Therefore, it may be difficult to determine which assessment approach to select. However, some examples of consensus guidance do exist, which may have common features that are widely applicable to the clinical trials arena.

The MATRICS initiative has worked towards a consensus cognitive test battery for schizophrenia using a series of meetings and evaluations of tests and finally, objective evaluation of a selected test battery. In working towards this consensus, the following essential criteria for a consensus cognitive battery for clinical trials in schizophrenia were agreed upon:

1. Reliable and valid assessment of cognition at the level of all individual major cognitive domains.
2. Inclusion of the following cognitive domains: Speed of Processing, Attention/Vigilance, Working Memory, Verbal Learning and Memory, Visual Learning and Memory, Reasoning and Problem Solving, and Social Cognition.
3. High test–retest reliability.
4. High utility as a repeated measure.
5. Demonstrated relationship to functional outcome.
6. Demonstrated tolerability and practicality.

The recent draft EMEA guideline on medicinal products for the treatment of Alzheimer's disease and other dementias makes a number of recommendations for cognitive assessment in recognising symptomatic improvement, which may consist in enhanced cognition, as one of the three main goals in the treatment of dementing conditions. These include: validation in the specific population under study (construct validity, test–retest reliability, inter-rater reliability, internal consistency, etc.); normative data to allow interpretation of results and clinical meaningfulness to be established; and batteries of tests which cover a number of domains of cognition (i.e. learning of new material, remote as well as recent memory, recall and recognition memory for various modalities including verbal and visuo-spatial, language, constructional ability, attention/concentration and psychomotor speed). Whilst in both examples, the specific domains covered and validation in the relevant clinical populations, are unique aspects, there are a number of common criteria which emerge. These are: assessment of cognition at the level of individual cognitive domains relevant to the population under study; validation in the population under study (test–retest reliability; inter-rater reliability, internal consistency); utility in the population under study; utility as a repeated measure; and data allowing interpretation of results and understanding of the clinical relevance (i.e. normative/relationship to functional outcome). Some of these important 'global' criteria will be outlined in more detail in the following sections.

The importance of assessment at the level of individual cognitive domains

The most commonly used assessments of IQ identified in the search of paediatric clinical trials published over the past year were the WISC and the WPPSI. Several versions of the tests exist and they have been extensively validated with respect to sensitivity (lack of ceiling and floor effects), reliability and age appropriateness of the material. Both assessments have primarily been used to derive scaled IQ scores by age, based on a series of subtests. However, the results of individual subtests are not often reported in the literature, and the use of IQ scores alone may fail to fully represent the nature of cognitive/neuropsychological impairment in some areas of research. It should be noted though, that the recently published WISC-IV has looked to address this issue with additional work on subscales assessing working memory and processing speed, which may have advantages over WISC-III, for example, in sensitivity to cognition impairment in ADHD [14].

In paediatric epilepsy, cognition and behaviour are seen as the most crucial determinants of outcome following seizure control [15]. Neuropsychological test performance has been shown to directly influence academic performance [16]. The use of antiepileptic drugs (AEDs) has itself been shown to be associated with cognitive impairment, which may then compound the effects of the disorder itself on learning and development [17]. In a review of the influence of seizure and AED exposure on normal brain development, Marsh *et al.* [18] conclude that there is evidence from several sources indicating that these two factors do adversely affect long-term cognition. Two other conclusions are also important to the discussion here: firstly, whilst there are data showing AEDs impair cognition in paediatric epilepsy populations and that AEDs have adverse effects on cognition in adults and in animal models, there is a paucity of neuropsychological assessment data in paediatric epilepsy post-1990; and secondly, that the common use of standard IQ assessments has limited the usefulness of some studies, as these data lack the sensitivity of more detailed neuropsychological assessments. This highlights two major research issues in paediatric epilepsy: the lack of cognition studies; and the lack of appropriate cognition assessments. As an example of the former, whilst topiramate has been shown to impair cognition in adults [19,20] and this is a concern in paediatric patients because of reported cognitive impairment/sedation [21] this has not been assessed objectively in the paediatric population. Therefore, objective evaluation of the relative cognitive risks and benefits for paediatric use is not possible. In respect of the latter, studies such as that by Cormack *et al.* [22], may be less informative than they could be in only reporting IQ scores. IQ assessments provide well validated, age appropriate measures, but typically do not measure specific cognitive domains, for example, psychomotor speed, attention, working memory, secondary memory, and may be less sensitive to change. In addition, these assessments typically lack validated translations, may be culturally specific, lengthy in duration and lack parallel forms. This may result in an incomplete picture of cognitive dysfunction, in that dysfunction may be under-reported, or differential cognitive effects may be missed (see Baker and Goldstein for a review of neuropsychological assessment in epilepsy [23]).

Deficits to attention are known to be important in patients with epilepsy, indeed impairment of attention has been found to be more

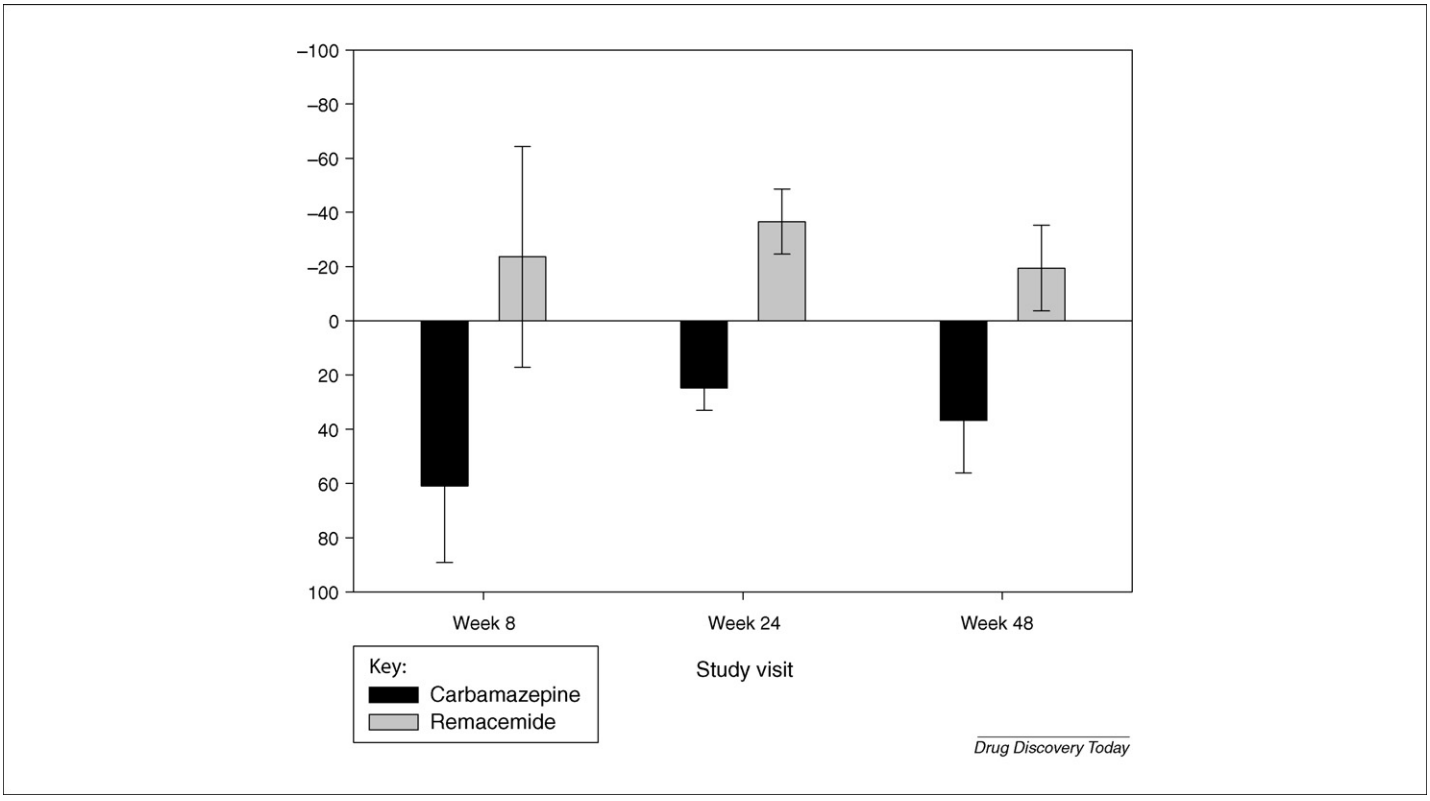

FIGURE 1

Attentional effects of carbamazepine versus remacemide during multiple dosing in newly diagnosed epilepsy. Mean (±SEM) change from pre-dose baseline in reaction time: power of attention measure (ms) from the CDR system.

significant in predicting academic failure than measures of memory or socioeconomic status [24]. Thus it is certain that this aspect of cognitive function must be properly addressed. The importance of attentional measures in clinical trials can be highlighted using data from the SEReNE trial, which compared the cognitive profiles of carbamazepine and remacemide in newly diagnosed adolescents or adults, aged 12–75 years, from 21 countries (within Europe, Latin America and Australasia; $n = 531$). Detailed methodology for the collection of efficacy data has been previously described [25]. Computerised cognitive function assessment using the cognitive drug research (CDR) system, brief, repeatable, modular, computerised battery designed to assess comprehensive and specific aspects of cognition in clinical trials [26,27] was performed at baseline (before receiving drug treatment) and then again at 8, 24, 48, 72, 96, 120, 144 and 168 weeks subsequent to beginning treatment. Overall, the comparison of remacemide with carbamazepine showed that of the two compounds, remacemide had a more beneficial cognitive side effect profile, which was most evident in measures of attention (Figure 1). Attention was a key discriminator in establishing the cleanest cognitive profile of the two compounds assessed. This finding is supported by the types of adverse events experienced by the patients (as reported by Brodie *et al.*) with fatigue and somnolence being more frequently reported by patients taking carbamazepine. To enable a comparison of the epilepsy patients, a normative sample was taken from the CDR Normative Database version 3.0 containing cognitive function performance data from over 5000 healthy volunteers, across an age range of 8–87 years of age. These data were even more relevant when considering the impairment to attention already evident in the children and adolescents in the study compared to age-matched normative data, which was an effect size of 0.63 (Table 1). An additional treatment related impairment of attention would then have the possibility of further adversely influencing academic performance in these patients.

Utility as a repeated measure

In clinical trials repeated assessment will be crucail to allow for measurement of treatment effects over time. Furthermore, the

TABLE 1

Effect size (*d*) of existing attentional impairment in newly diagnosed paediatric epilepsy (12–17-year olds)

Variable	Age band	Epilepsy			Healthy normative sample			Millisecond deficit in reaction time	Effect size (*d*)
		N	Mean	SD	*N*	Mean	SD		
Power of attention (millisecond reaction time)	12–17	92	1315	202.3	21	1194	146.4	121	–0.63

benefits of multiplying repeating tests over a single day to characterise peak and duration of effects for safety or PK/PD modelling, and the ability to repeat tests several times during multiple dosing to compare acute effects to steady state, or conduct interim assessments to allow for patient attrition, should not be underestimated. This type of repeated assessment requires that tests have multiple parallel forms, with equivalent but different test stimuli at each administration. Without this, over-learning may result in ceiling effects preventing a test from detecting improvement, or treatment effects on learning may be confounded with those on other aspects of cognition [28]. It is also necessary that the tests are relatively brief so that repeated assessment, if feasible within a study, and test batteries themselves, are not overly fatiguing. The potential benefits of this type of repeated assessment in children can be seen from a number of studies investigating pharmacotherapy in attention deficit/hyperactivity disorder. The laboratory school protocol [29] was designed to allow for repeated assessment of school children with ADHD, allowing for well-controlled activities which may be repeated across a day and over several days within a study. One of the specific applications is to allow for pharmacokinetic and pharmacodynamic assessment, allowing a profile of effects over time and peak effect to be assessed for a given treatment. Other studies have used repeatable cognitive assessments to look at dose response [30] as well as compare treatments across the day for efficacy, speed of onset and duration of action [31–33]. In this way assessments specifically designed to be multiply repeated over shorter durations can add valuable information to the drug development process by providing a much more detailed understanding of (relative) efficacy.

Validation

A number of statistical/psychometric properties are important features of assessments suitable for research requiring repeated measures. These repeated assessments should be well related (test–retest reliability), show stability, have good inter-rater and/or intra-rater reliability where appropriate, show concurrent validity (association with measures assessing the same functions), construct validity (e.g. demonstrated through factorial analyses) and sensitivity (in particular pharmacosensitivity for clinical trials use). It is crucial that these properties are established in the population under study, as these properties may not hold across populations, for example, language, cultural or disease specific factors may all have some influence. With particular relevance to paediatric studies is the importance of age-specific evaluation, which is covered further in the next section.

As one example of these properties, the importance of thoroughly evaluating test–retest reliability is often over looked. Test–retest reliability is often reported as 'good' in assessments of test properties, but publications rarely define what good is. Therefore, an important factor in test selection is to assess test–retest relative to other assessments, and also to recognise that this property may not hold across subtasks and measures within a battery, or across different populations, such as different age groups and clinical groups. Reliability of 0.7 has been recommended as a minimum when comparing between groups [34–36]. Mahone has reviewed psychometric properties for a number of attentional assessments in preschool children (<6 years) [37]. This review demonstrates that these computerised tests of attention can be employed to provide meaningful data in children aged as young as 3. However, psychometric properties did vary considerably, with some measures demonstrating acceptable test–retest reliability in excess of 0.7, but others showing test–retest to be as low as 0.5, and for one individual measure less than 0.2. Whilst these data demonstrate that a range of assessments including computerised approaches possible even in young children, the importance of evaluating psychometric properties when selecting assessments is also illustrated; the consequence of using tests with low reliability being a loss of sensitivity/increase in sample size.

Importance of normative data

Normative data on assessments is crucial for three reasons: it is essential for evaluation of psychometric/statistical properties as described above; in study design, for sample size/power considerations; and for meaningful interpretation of study data. Unless a study is being run as a pilot for hypothesis generation, or assessments are treated as adverse event data and summarised as frequency of incidence and probable relationship to drug, it will be important to state clearly the hypotheses to be tested for proof of concept/proof of efficacy. This requires existing data in order to select effect size(s) and associated variance, on which to base sample size calculations. Without this information studies risk either being underpowered, or generating statistically significant effects, which do not have clinical relevance. Furthermore, when attempting to assess the relevance and importance of possible effects on cognition at the end of the study, normative data showing what would typically be expected of children at a particular age is important. For example, should a compound preferentially impair or enhance specific domains or measures of cognition, it will be important to relate this to the drug-free profile of cognition in the patients studied, which can be derived by comparison to appropriate normative data. This allows questions such as: is a cognition enhancer influencing relevant aspects of cognition? or are treatment related side effects occurring in areas of cognition, which are already impaired? to be answered, as in the above example of attention deficits in epilepsy. ICH guideline E11 describes the importance of age categorisation to account for developmental changes, but also makes the point that subjects may move between categories during a study. These age categories (defined in completed days, months or years) are:

- Preterm newborn infants
- Term newborn infants (0–27 days)
- Infants and toddlers (28 days to 23 months)
- Children (2–11 years)
- Adolescents (12 to 16–18 years)

These categories are acknowledged as arbitrary, and it can be seen from cognitive data (Figure 2) that performance ability may change markedly within a category. However, the importance of detailed normative data in characterising data against normal developmental profiles is clear.

Automation of test batteries

Use of electronic data capture (EDC) and to a lesser extent electronic data transfer (EDT) are increasing within the pharmaceutical industry. The benefits of these approaches include time and cost savings, reduction of data queries, elimination of paper costs and

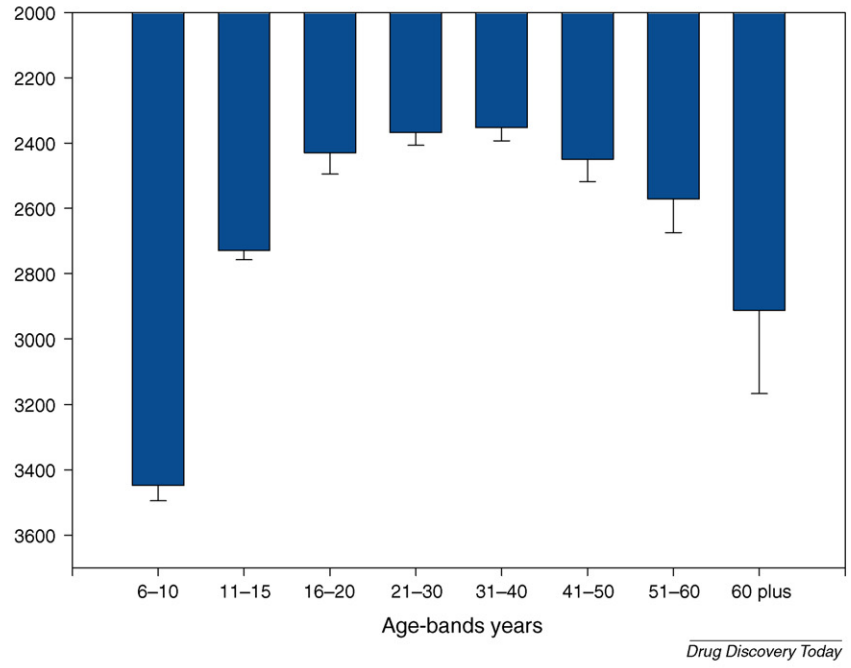

FIGURE 2

Effects of ageing on reaction time over the life span. Mean (±SD) combined reaction time measure (ms) from the CDR system.

reduction in monitoring costs, which may lead to 30% greater efficiency in clinical trial duration, 43% in time to database lock and 86% in number of queries [38]. Specific to cognitive/neuropsychological assessment, the use of automated procedures allows for presentation of test stimuli to be standardised, allows for capture of accurate and precise reaction time data and for standardisation of scoring procedures, all of which are purported to improve sensitivity and psychometric/statistical properties of assessments. However, there are clearly populations or situations where automated assessment may not be appropriate, such as those with physical disability, severe forms of dementia/cognitive impairment, or very young children, who may not be able to interact with a computer. In addition, there are other concerns regarding the use of automated tests. For example, when developing the MATRICS consensus criteria some clinicians argued for paper-and-pencil measures citing two primary advantages: first, subjects are better able to attain optimal test performance via establishment of clinical rapport and second, interpretation of test data is enriched through access to qualitative observation of test behaviour. In addition, it was noted that computerised tests were 'frequently associated with loss of data because of computer malfunction or problems in saving, retrieving, and reading data files'. It seems probably that the experiences giving rise to this last point are related to a further aspect of validation, which is regulatory as opposed to scientific validation. The guidance 21 Code of Federal Regulations (21 CFR Part 11) Electronic Records; Electronic Signatures, covers those aspects of computer systems validation, which guarantee against the data loss that may be associated with non-compliant systems. This aspect of validation should probably be given equal weight to the scientific validation, as even the best test poorly applied will have little value.

In summary then, there are three broad issues related to use of automated test batteries. There are clearly substantial efficiencies to be made through use of automated assessment. Therefore, it is prudent that these approaches be evaluated in a drive to reduce the public cost and time associated with the development of drug treatments. However, automation is no guarantee of utility or validity in a given population, and these are properties which must be established empirically, and compared between assessments. Lastly, automated test selection for clinical trials should look to regulatory validation in addition to scientific validation, to ensure appropriate standards are met.

In conclusion, there are clear benefits to the assessment of neuropsychological test performance in infants, children and adolescents, during the drug development process. These assessments allow for cognitive and developmental safety issues to be assessed in populations particularly vulnerable to potential adverse effects, because of possible influences on development and academic achievement, but also provide potential efficacy measures in populations with pre-existing cognitive impairment. These assessments are a crucial addition to self-report and subjective assessments, which may differ from objective measures, because of under- or over-reporting of symptoms, lack of awareness in children, or as a result of impaired cognition. Thorough neuropsychological assessment confers distinct advantages over IQ assessment alone, by allowing assessment of a cognitive profile, including individual domains such as attention and memory to be measured separately. This detailed assessment is important because of the possibility for pre-existing cognitive impairment and drug effects to have differential effects on cognition. Furthermore, the use of tests specifically designed to allow for repeated assessment can provide detailed information about dose response,

speed of onset, duration of effect and other information important in evaluating efficacy. Lastly, the flexibility to assess wider populations for example to allow for the possibility of multi-site, multinational clinical trials makes well-designed tools easier to apply in the clinical trials setting. These kinds of scientific and operational benefits can be further optimised by the use of computerised cognitive test batteries specifically designed for clinical trials use, with the ability to simplify and improve administration, capture and transfer data electronically, and record reaction time data. Computerised cognitive tests and test batteries can be employed in infants, children and adolescents, to give brief, stable, reliable and sensitive assessments of cognition. However, no assumptions should be made about the appropriateness of a test without first evaluating the psychometric and statistical properties in the population to be studied. Neither prevalence of use nor automation of procedures provides any guarantee of suitability, and much effort is required in the evaluation and selection of measures to ensure studies are well designed and that maximum benefit is derived from the data. Paediatric clinical trials will benefit from employing cognitive test batteries, which have been properly evaluated for their psychometric properties and which have available comprehensive normative data.

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