An Individualized Approach to Tracking and Treating Alzheimer’s Disease

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There can be substantial variation in the expression of Alzheimer’s disease. Patients vary in who is affected (e.g., education, age at onset), in how they are affected (e.g., neuropathological profile, comorbidities), and in when they present (i.e., stage of illness). Even people with similar starting profiles can have dramatically different courses. For these reasons, tracking disease progression in individuals and the effects of treatment on them can be challenging. This variability further complicates the difficulty of dementia’s high dimensionality—Alzheimer’s disease affects many aspects of cognition, function, and behavior.

Clinical trials in Alzheimer’s disease have addressed heterogeneity in two ways. One employs judgment-free standardized tests in various domains (e.g., cognition, quality of life). The other uses judgment-informed global clinical measures, which require varying degrees of individualization. Completely individualized approaches have proven to be challenging, despite their potential for efficient dimensionality reduction. Recently, software to enhance individualized assessment and symptom tracking in Alzheimer’s disease has been developed. This article details the challenge of individualization and reviews how Web-based methods can address some of these challenges and facilitate the elucidation of patient–caregiver perspectives in dementia and its treatment.

Alzheimer’s disease, the most common cause of dementia, progressively affects cognitive function. The clinical expression of Alzheimer’s disease can vary substantially between individuals. Variable disease expression arises because individuals have different levels of premorbid education and intelligence, have varying neuropathological changes and comorbid conditions, and present at different stages of their illness. Operating within a framework of diagnostic criteria, clinical diagnosis therefore must be judgment-based and must take into account both all these sources of individual variability and the cultural context in which a cognitive complaint is evaluated.

Variable disease expression is also a challenge to discerning the effects of treatment. This is all the more so because even people with apparently very similar starting profiles can have dramatically different disease courses. Furthermore, dementia by definition is a global cognitive impairment that is severe enough to affect social and occupational functioning. This means that dementia has several dimensions, typically affecting many aspects of cognition, function, and behavior.

Dealing with the high dimensionality of Alzheimer’s disease expression has been a particular challenge in clinical trials.1 Early on, the US Food and Drug Administration recognized the need to balance the many factors that might make up a successful treatment effect. In 1990, it required that clinical trials in Alzheimer’s disease have two primary outcomes. One would be a standardized neuropsychological test battery, which until now has largely been the Alzheimer’s Disease Assessment Scale–Cognitive Subscale (ADAS-Cog). The ADAS-Cog evaluates several cognitive domains, although with notably little assessment of executive function. The second primary measure was a judgment-based, individualized global clinical scale. Initially, clinicians were asked to conduct an interview with the patient and then use a seven-point change scale, anchored at 4 (which indicated no change) and ranging from 1 (very much better) to 7 (very much worse). This evolved into another instrument, the Clinician’s Interview-Based Impression of Change, Plus Caregiver Input (the CIBIC-Plus). It too has tended to be widely used, although sometimes the Clinical Dementia Rating, a semi-individualized staging measure that ranks people in five domains, is employed in its place.2 Over time, some decision makers in clinical trials have sought to standardize the CIBIC-Plus by specifying which domains should be evaluated and how they should be scored. This worry about the seeming subjectiv-

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ity of individualized measures has also motivated the push for biomarkers as outcome measures in clinical trials. Among many reasons to be skeptical of relying only on standardized measures and biomarkers, an important one is that they lack inherent clinical meaningfulness. Clinical meaningfulness in dementia has itself received comparatively little empirical study. Instead, the field has tended to rely on the consensus of experts; commonly this amounts to the view that a four-point change in the ADAS-Cog (which would be the average amount of decline over about 6 months in untreated patients) should constitute a clinically meaningful effect. Compared with clinically meaningful measures, the four-point change has been found to be useful in distinguishing group effects but also to result in substantial individual misclassification of patients’ treatment responses.1

One approach to discerning the effects of treatment requires patients and their families, at the beginning of the trial, to set both goals for treatment and plausibly better and worse outcomes (Table 1). The extent to which these goals are attained is then measured. The extent of goal attainment is scored in a formula that corrects for differential weighting of goals and differing numbers of goals between patients. (Most patients set between three and six goals.) The formula has been adapted so that a score of 50 is the baseline state, >50 indicates improvement, and <50 means worsening. In a double-blind trial, whatever the effects of subjectivity of individualized measures are, they should be balanced in the treatment groups. In consequence, a statistically significant difference in goal attainment should be inherently clinically meaningful, all other things being equal.

Table 1 Examples of two goals (out of four) in a 76-year-old woman with mild dementia

<table>
<thead>
<tr>
<th>Goal-attainment level</th>
<th>Goal title: Repeating questions</th>
<th>Goal title: More initiation of activities</th>
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<tbody>
<tr>
<td>+2 Much better than baseline</td>
<td>On most days, repeats the same question only one or two times per dayb</td>
<td>Initiates interactions with other people from the complex, with encouragement from her husband</td>
</tr>
<tr>
<td>+1 Somewhat better than baseline</td>
<td>On most days, repeats the same questions fewer than 10 times a day, and without alarm or anxiety</td>
<td>Initiates more activities with her husband (e.g., suggests that they do something other than go out for coffeeb)</td>
</tr>
<tr>
<td>0 Baseline</td>
<td>Every day, asks her caregiver the same questions, about 10 times per day, usually in relation to things that are going to happen. For example: “Where is the phone? When do we see Dr. ____ next?” Will repeat within 10 minutes of having asked last, usually seeming very anxious, even alarmed, about the answer</td>
<td>Talks about participating in social activities (wants to) but refuses to do anything about it. Wants to get together with other women in the complex but won’t introduce herself (been there 6 months). Likes to go out for coffee with her husband and initiates same (daily). All other activities are planned by her husband</td>
</tr>
<tr>
<td>−1 Somewhat worse than baseline</td>
<td>Repeats questions more often (15–20 times per day) but still at least 10 minutes apart</td>
<td>No longer initiates coffee outing with husband but still willing to go</td>
</tr>
<tr>
<td>−2 Much worse than baseline</td>
<td>Repeats questions almost immediately or within 5 minutes of last asking, OR, without an increase in frequency, becomes frankly agitated about the answer</td>
<td>Needs encouragement to go on outings with husband and sometimes refuses to go or, having arrived, demands to leave</td>
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*Goals are ranked in terms of relative importance; the most important goal is ranked highest (e.g., four out of four goals). The attainment level achieved at follow-up (here, 4 months after the baseline visit).

Note that the goals can mix frequency and intensity of symptoms and are semiquantitative. They also allow for some observed variability.

Table 2 Descriptors of two common dementia symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Descriptors</th>
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<tbody>
<tr>
<td>Memory of recent events</td>
<td>Forgets the details of a recent event but recalls the event Forgets that recent events occurred Forgets everyday events but retains more novel or important information Forgets someone’s name shortly after being introduced Forgets conversations shortly after they occur (e.g., within the hour) Forgets the original topic of conversation Forgets information shortly after reading it Forgets how she or he arrived somewhere Cannot remember if a task was performed Cannot follow through on a task, forgets what she or he already did</td>
</tr>
<tr>
<td>Social interaction/ withdrawal</td>
<td>Will take part in, but no longer initiates, outings or social activities Will go to a social event but then wants to leave right away Is reluctant to go on outing or attend social functions Participates less in family events (e.g., Sunday dinner, worship activities) Wanders off or sits alone during social activities, gatherings, or events Rarely initiates conversations with others Actively listens but does not contribute to conversations Is timid or anxious around unfamiliar people Is timid or anxious around groups of people, even people they know Takes part less often in volunteer and community activities Has stopped taking part in volunteer and community activities Makes excuses as to why he or she can’t go places Restricts who they will see/only wants to see certain people</td>
</tr>
</tbody>
</table>

Patients/families use these as prompts and personalize the items that they choose to set goals. © DementiaGuide Inc., 2006. Used with permission.
Setting goals and measuring their attainment using goal-attainment scaling (GAS) has proved to be feasible, valid, and responsive in dementia. Even so, many people find it hard to complete a goal-attainment follow-up guide. To help with setting individual goals and thereby allow the perspectives of patients and families to inform the measurement of treatment effects, Web-enabled software, called the SymptomGuide, has been developed. The SymptomGuide provides information on about 70 dementia symptoms, across the spectrum from mild to severe dementia. The information includes about a dozen plain-language descriptions of symptoms, using terms that are often employed and readily understood by patients and families. Typically, the symptom descriptors span a range from the types of problems that would be present in someone with mild dementia to those that would be present in a patient in whom dementia was severe. Used in a clinical trial, the SymptomGuide can help patients and caregivers to describe their current problems. Also, reading the range of descriptions of each problem will help them better understand how problems might worsen or improve. In this way, the descriptions can allow more ready understanding of what is needed in the goal-attainment follow-up guides and thereby more rapid completion of them (Table 2).

Even with such guidelines to goal setting, it is important to note that in a clinical trial the inference allowed by the summary score is simply the extent to which goals have been attained. What the GAS formula does not do is to indicate which goals were met, although this can be done in subsequent analyses, including qualitative studies.

GAS is an individualized measure, meaning that it seeks to characterize by distinctive qualities and to particularize by making goals obviously related to a specific person. In consequence, patients will not be judged according to the same standard set of goals but by their own goals. This is viewed by some as an inherent weakness, because it seems arbitrary. Yet it is essential for individualization, which, as we have seen, has been accepted in dementia drug evaluation from the outset. Note too that in a randomized, blinded trial there is no reason for systematic bias in goals to occur, although this can happen by chance, as do other sources of bias (e.g., chance misassignment with respect to stage, or sex, or age). As with any of these considerations, imbalance in goals can be evaluated empirically, post hoc. There is no reason, however, that goals should be more susceptible to the play of chance than other factors are.

Similarly, a randomized, double-blind design is a remedy for worries about individualized measures. Other such concerns include that they are susceptible to fraud or “gaming” (e.g., setting goals that are too easy to achieve) or that just a few items drive the treatment effect. Again, these factors are not unique to individualized measures and would be the case for new standardized measures.

The amount of time required by GAS is “front-end loaded.” Typically, a half-hour interview at the outset is needed to establish goals, but follow-up takes much less time. In clinical trials, time can be saved when the GAS interview is carried out by the CIBIC-Plus rater because it can save time with the CIBIC-Plus interview as well. Feedback from studies with GAS suggests that patients and caregivers value being able to provide input, so an individualized measure can help ensure overall adherence to the testing protocols. Note that GAS also has the advantages of less cultural bias (by setting goals, patients and caregivers can ensure that the goals are appropriate to their cultural context) and facilitation of knowledge translation (giving clinically recognizable patterns).

GAS and other individualized measures also allow other perspectives to be brought to bear on what constitutes effective treatment, which can in turn lead to a better understanding of disease processes. For example, when the first Alzheimer’s disease trials were established, the view was that it was chiefly a disease of the mesial temporal lobes, with frontal function affected late in the illness. The very first experience with GAS in an Alzheimer’s disease trial made clear, however, that patients and caregivers were very interested in executive function and that there was an important signal to be detected there. Thus far, GAS has been used in trials of up to only one year in duration. Longer trials would need to allow for emergence of new, troublesome symptoms. These can readily be accommodated, being recorded as “less than expected” outcomes. To date, to be conservative, unexpected improvements have not been recorded as new goal areas (with “better than expected” outcomes), but in principle this too could be done.

In summary, individualized outcome measures in dementia offer the potential to complement standardized evaluations with assessments that can enhance our understanding of clinical meaningfulness and give patients and caregivers a voice in testing whether treatments work. By making individualized measurement more feasible, Web-enabled software can help close a gap in the current drug testing process and do so at a time when the number of countries and cultural contexts in which dementia treatment is being evaluated is growing. The perspectives of patients and caregivers can also identify unanticipated treatment effects, thereby also allowing a better understanding of the science of dementia. These potential effects require additional testing of individualized measurements and supporting software, which can be added to existing standardized measures in clinical trials in dementia.

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CONFLICT OF INTEREST
The software described in this article has been commercialized by DementiaGuide Inc. (DGI), of which the author is president, chief scientific officer, and majority shareholder. DGI commercializes the author’s work on individualized outcomes measurement in dementia.
The Impact of the Orphan Drug Act on the Development and Advancement of Neurological Products for Rare Diseases: A Descriptive Review

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Many neurological diseases or conditions are rare disorders. The Orphan Drug Act (ODA) of 1983 was promulgated to promote the development of products for such conditions. In this Opinion piece, we discuss how the ODA has affected neurological diseases, note how current and future sponsors (any person(s) or entity (i.e., academic, corporate body, individual, manufacturer) that applies for an official regulatory action) of products for rare neurological diseases can take advantage of ODA incentives, identify areas of success and continuing needs, and review data that can help drive the future development of products for rare neurological conditions.

The 1983 Orphan Drug Act (ODA; Pub. L. no. 97-414) has had a tremendous impact on the availability and advancement of products for rare diseases and conditions.¹ This piece of legislation was put forth primarily to stimulate the future development of products for rare neurological conditions. In this opinion piece, we discuss how the ODA has affected neurological diseases, note how current and future sponsors (any person(s) or entity (i.e., academic, corporate body, individual, manufacturer) that applies for an official regulatory action) of products for rare neurological diseases can take advantage of ODA incentives, identify areas of success and continuing needs, and review data that can help drive the future development of products for rare neurological conditions.

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