Treatment dose in post-stroke aphasia: a systematic scoping review

Sam R. Harvey, MSpPath\textsuperscript{a,b}, Marcella Carragher, PhD\textsuperscript{a,b}, Michael Walsh Dickey, PhD\textsuperscript{b,c,d}, John E. Pierce, BSpPath\textsuperscript{a,b}, and Miranda L. Rose, PhD\textsuperscript{a,b}

\textsuperscript{a}School of Allied Health, Human Services and Sport, La Trobe University, Melbourne, Australia; \textsuperscript{b}Centre of Research Excellence in Aphasia Recovery and Rehabilitation, Australia; \textsuperscript{c}Geriatric Research Education and Clinical Center, VA Pittsburgh Healthcare System, USA; \textsuperscript{d}University of Pittsburgh, USA

Sam R. Harvey. Health Sciences 1, La Trobe University, Plenty Road, Bundoora 3083, Australia. ORCID identifier: 0000-0002-4839-2117 Twitter: @SRHarvey_

sam.harvey@latrobe.edu.au

Marcella Carragher. Health Sciences 1, La Trobe University, Plenty Road, Bundoora 3083, Australia. ORCID identifier: 0000-0002-7200-6968 Twitter: @MarcellaC_SP

marcella.carragher@latrobe.edu.au

Michael Walsh Dickey. 6077 Forbes Tower, University of Pittsburgh, Pittsburgh PA 15260, USA. ORCID identifier: 0000-0002-9068-3313 mdickey@pitt.edu

John E. Pierce. 2-6 Hopetoun Street, Elsternwick 3185, Australia. ORCID identifier: 0000-0001-5164-5106 Twitter: @johnpierce85 pierce.john.e@gmail.com

Miranda L. Rose. Health Sciences 1, La Trobe University, Plenty Road, Bundoora 3083, Australia. ORCID identifier: 0000-0002-8892-0965 Twitter: @rose_mirandaros

M.rose@latrobe.edu.au

Corresponding author:

Professor Miranda Rose, PhD
Treatment dose in post-stroke aphasia

ABSTRACT

Little is known about how the amount of treatment a person with aphasia receives impacts aphasia recovery following stroke, yet this information is vital to ensure effective treatments are delivered efficiently. Furthermore, there is no standard dose terminology in the stroke rehabilitation or aphasia literature. This scoping review aims to systematically map the evidence regarding dose in treatments for post-stroke aphasia and to explore how treatment dose is conceptualised, measured and reported in the literature. A comprehensive search was undertaken in June, 2019. 112 intervention studies were reviewed. Treatment dose (amount of treatment) has been conceptualised as both a measure of time and a count of discrete
Treatment dose in post-stroke aphasia

therapeutic elements. Doses ranged from one to 100 hours, while some studies reported
session doses of up to 420 therapeutic inputs per session. Studies employ a wide variety of
treatment schedules (i.e., session dose, session frequency, and intervention duration) and the
interaction of dose parameters may impact the dose-response relationship. High dose
interventions delivered over short periods may improve treatment efficiency while
maintaining efficacy. Person- and treatment-level factors that mediate tolerance of high dose
interventions require further investigation. Systematic exploration of dose-response
relationships in post-stroke aphasia treatment is required.

Word count: 5,884 (including abstract, tables headings, figure captions, and
citations; excluding abbreviation list, bibliography, figure legend, and appendices)

Keywords: Aphasia; stroke; treatment; rehabilitation; dose; scoping review

Abbreviations

CIAT Constraint-Induced Aphasia Therapy
ICAP Intensive Comprehensive Aphasia Program
ICF International Classification of Functioning, Disability, and Health
M-MAT Multi-Modality Aphasia Therapy
NHMRC National Health and Medical Research Council
PRISMA Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-ScR PRISMA Extension for Scoping Reviews
RCT Randomised Controlled Trial
SCED Single-case experimental design
SFA Semantic Feature Analysis
TIDieR Template for Intervention Description and Replication
Treatment dose in post-stroke aphasia

Aphasia is a significant acquired language impairment affecting 30% of stroke survivors.\textsuperscript{1} Recovery is highly variable and difficult to predict with aphasia persisting as a chronic condition in up to 50% of cases.\textsuperscript{2-4} Aphasia is associated with a 2-fold increased risk of mortality,\textsuperscript{5} higher healthcare costs,\textsuperscript{6} negative consequences for personal relationships, social integration, and economic independence,\textsuperscript{3,7} and is associated with poorer quality of life than many other debilitating health conditions including Alzheimer’s disease and cancer.\textsuperscript{8} Treatments are needed to reduce the impact of aphasia.

Aphasia treatments may aim to remediate symptoms of language processing impairment (e.g., anomia, agrammatism) by targeting specific linguistic functions (e.g., word retrieval, syntactic processing).\textsuperscript{9} Alternatively, intervention may aim to improve how a person communicates with others using pragmatic, functional communication, and social interaction approaches.\textsuperscript{9} Results of meta-analyses demonstrate the effectiveness of interventions targeting language impairment, communication activity and participation, and communication-related wellbeing.\textsuperscript{10-13} However, little is known about how the amount of treatment a person with aphasia receives impacts aphasia recovery following stroke. This knowledge is vital to improve healthcare efficiency and quality of life for people living with aphasia.

Quantifying aphasia interventions

Defining dose

There is no consensus definition within the stroke rehabilitation literature to describe the amount of treatment a person receives, nor has standard terminology been established in the aphasia literature.\textsuperscript{14,15} Attempts to investigate “dose articulation” within pre-clinical and clinical stroke rehabilitation studies are underway.\textsuperscript{16} In the aphasia domain, the terms dose, dosage, and intensity are commonly used interchangeably to refer to divergent concepts; for
Treatment dose in post-stroke aphasia

example, the number of repetitions within a specific therapy task, the duration and number of
sessions, the overall duration of a treatment program, the total number of treatment hours
provided over the course of an intervention, or the effort required to successfully complete a
task.\textsuperscript{14, 15, 17} The lack of consensus definitions and inconsistent use of these terms confounds
attempts to examine the individual contribution of each parameter to overall treatment
effectiveness.\textsuperscript{17}

\textit{A way forward}

The taxonomy proposed by Warren, Fey, and Yoder\textsuperscript{18} and elaborated by Baker\textsuperscript{14} provides
one definition and delineation of dose and intensity parameters for behavioural interventions
(Figure 1). This model is gaining traction in the aphasia treatment literature,\textsuperscript{17, 19, 20} but is not
yet widely accepted.

The key assertion of this taxonomy is that the amount of therapy provided or received
is a product of the number of times the active ingredients of a particular treatment are applied
over the course of the treatment schedule. Active ingredients are “the procedures presumed
by the interventionists to teach or enhance new learning and behaviour”.\textsuperscript{18} Closer
examination of the quality and quantity of active ingredients may ultimately enhance our
understanding of the mechanisms of action that transform received therapy into improved
health and wellbeing.\textsuperscript{21} Once identified, maximising delivery of active ingredients has the
potential to increase treatment efficiency and effectiveness.

\textbf{Figure 1 Model of dose and intensity parameters involved in determining optimal
intervention intensity}\textsuperscript{14} (reproduced with permission)
Treatment dose in post-stroke aphasia

Definitions used in this review

In the absence of consensus definitions but informed by the above taxonomy, the following definitions have been adopted for this review:

Therapeutic element
The basic unit of therapy; either a therapeutic input or a client act

Session dose
A quantitative measure of the therapeutic content provided in a session, in minutes or therapeutic elements

Total dose
The number or quantity of doses provided or received over an intervention period e.g., total hours, total number of therapeutic elements

We note that the term ‘intensity’ has commonly been used to refer to session frequency.\textsuperscript{14, 18} While treatment intensity is not the focus of this review, it is acknowledged that it is often not possible to discuss dose without reference to intensity.\textsuperscript{22} Further, Warren and colleagues and Baker use cumulative intervention intensity for what we will refer to as total dose.\textsuperscript{14, 18}

Measuring dose
Given the lack of consensus definitions, it is unsurprising that a standard basic unit of dose in aphasia interventions has yet to be established. The prevailing convention in aphasia research and clinical practice has been to measure total dose in number of hours or sessions provided or received\textsuperscript{12, 23}. Hours of therapy is a convenient measure; it is easy to capture, calculate, and compare from one study to the next, has clinical relevance to service providers, is easily
Treatment dose in post-stroke aphasia

understood by consumers and health policy makers, and satisfies minimum reporting standards (e.g., TIDieR Item 824).

However, measuring the amount of aphasia intervention in hours is inadequate because of the inherent assumption that all hours of therapy are equal. In standard care, intervention often targets several language and communication goals concurrently. Different goals may require different treatment approaches. Ultimately, one hour of treatment may comprise a variety of different tasks.25 Furthermore, one study found that direct therapeutic input accounted for only 57% of the intervention session.26 Unless treatment details are clearly reported and monitored, it is difficult to draw conclusions regarding how often different elements of therapy are being provided. Similarly, the rise of Intensive Comprehensive Aphasia Programs (ICAPs) sees delivery of multifaceted interventions where treatment targets and approaches purposively vary from session to session.27 Measuring the total dose of complex interventions, such as ICAPs, in hours makes it impossible to examine responses to specific therapeutic elements.

Optimal dose

Determining the optimal amount of treatment is an important component of stroke rehabilitation planning and provision.28 The term optimal conveys aspects of both efficacy and efficiency; the notion of maximal improvement in the minimal amount of time within the constraints of the clinical environment, while meeting patient and clinician expectations of recovery. Currently, clinicians have very little empirical guidance regarding optimal therapy dose across the breadth of communication disorders.29

Within the realm of aphasia, evidence suggests there is a range of doses that will result in positive treatment effects. In 2003, Bhogal and colleagues synthesized the existing evidence to investigate the impact of aphasia treatment intensity on recovery of language and
Treatment dose in post-stroke aphasia

communication functions; studies that demonstrated a statistically significant positive
treatment effect provided a total of 98.4 hours of therapy or more, whereas ineffective studies
provided a total of 43.6 hours of therapy or less. Although based on few studies, many of
which confound intensity and dose parameters, this finding lead to the assumption that “more
is better” and has heavily influenced the ongoing examination of dose-response relationships
in aphasia research. Several meta-analyses have also demonstrated larger treatment effects
with greater amounts of therapy. The current clinical reality, however, is that few people
will receive 100 hours of intervention due to many factors intrinsic and extrinsic to the
treatment recipient.

Treatments provided at lower doses (i.e., fewer hours) have been developed and are
efficacious. For example, treatment efficacy has been demonstrated after 30 hours of multi-
modality aphasia therapy (M-MAT), constraint-induced aphasia therapy (CIAT), and
ICAPs where intervention can be provided in either a massed or distributed treatment
schedule.

The reality is that different therapy targets may require different amounts of treatment
delivered at different rates to optimise recovery. For example, optimal gains in naming
accuracy may be achieved with a smaller dose of naming treatment as compared to optimal
gains in discourse-level auditory comprehension following conversational therapy. At a
theoretical level, picture naming in anomia involves stimulation of a relatively simple
psycholinguistic process which maps lexical representations to phonological forms involving
a relatively discrete neurological network, whereas auditory comprehension in discourse is a
far more complex cognitive-linguistic task involving large swathes of both cerebral
hemispheres. Furthermore, individual variation in post-stroke aphasia recovery underlines
the importance of careful attention to person-level factors that may predict treatment
Treatment dose in post-stroke aphasia

Determining optimal treatment dose for an individual person with aphasia therefore depends on many person- and treatment-level factors. In summary, treatment effectiveness has been demonstrated over a range of doses which raises a number of important questions. Are lower-dose interventions sufficient or should we expect a greater magnitude of improvement with increased dose of these interventions? Given the literature reported above, at which dose between 30 and 100 hours of a given intervention should we expect optimal recovery for a given individual? What person-level and treatment-level factors are likely to mediate dose-response in aphasia interventions? The answers to these questions will depend on the nature of the relationship between efficacy and dose and, potentially, between efficacy and each independent dose parameter (i.e., session dose, session frequency, and intervention duration).

To improve aphasia recovery we need to understand, investigate, and optimise the therapeutic mechanisms that are driving the brain and behavioural change. Ultimately, there is a pressing need to find more efficient delivery models to allow rapid recovery to acceptable levels for individuals with aphasia. Treatment dose is an important factor that requires immediate systematic investigation.

**AIMS**

A systematic scoping review was conducted in order to systematically map the evidence regarding treatment dose in post-stroke aphasia and to explore how dose is conceptualised, measured and reported in the aphasia intervention literature.
METHODS

Design

The scoping methodology described by Arksey and O’Malley was adopted as it enables mapping of key concepts underpinning an emerging research area and allows clarification of working definitions and conceptual boundaries of the topic. Additional considerations were drawn from a number of sources to enhance methodological rigour. The PRISMA-ScR checklist was referenced to ensure comprehensive and systematic reporting of the review.

Identifying the research question

Two questions drive this review:

1) In the post-stroke aphasia literature, how is treatment dose conceptualised, measured and reported?

2) Is there sufficient evidence in the post-stroke aphasia treatment literature to conduct meta-analysis on the effect of differing doses on treatment outcomes?

Identifying relevant studies

A comprehensive and systematic search was undertaken in June, 2019 for peer-reviewed randomised controlled trials, quasi-experimental studies, single-case experimental design studies, and case studies which report measures of quantity of behavioural aphasia therapy and aim to investigate the effect of that intervention on language impairment and communication activity/participation for adults with aphasia following stroke.

Using the Preferred Reporting Items for Systematic reviews and Meta-Analysis Guidelines (PRISMA), the following databases were searched, with no language or date limits set: PubMed, Medline, EMBASE, CINAHL, PsycINFO, and Cochrane Library. Table 1 shows search terms relating to post-stroke aphasia, intervention, and dose identified from
Treatment dose in post-stroke aphasia

relevant literature. These search domains were combined using the AND operator, and the
terms within each domain combined using OR. Search terms were modified in line with
individual database subject headings. An example of the final search strategy is provided in
Appendix 3. Reference lists of included studies were examined to identify additional studies
not captured during the systematic search.

Table 1 Search terms relating to treatment dose in aphasia

Selecting studies

Figure 2 shows a PRISMA flow diagram detailing the results of study identification,
screening, eligibility, and inclusion. The search yield was imported into citation software and
duplicates removed using software and manual checking. Titles and abstracts were then
screened by the first author as per the inclusion criteria to determine eligibility for full text
review. Twenty percent of full texts were double-screened by a second reviewer (author J. P.)
for inclusion, achieving 95% agreement between reviewers. Inconsistencies were discussed
and resolved, and inclusion criteria refined to improve application of inclusion/exclusion
criteria.

Figure 2 PRISMA flow diagram showing the study selection process

Eligibility criteria

Studies inclusion criteria:

• Full text peer-reviewed journal article in English
• Includes adults presenting with aphasia, at any time after stroke
Treatment dose in post-stroke aphasia

- Reports primary data from behavioural treatment(s) targeting language impairment or communication activity/participation
- Measures and reports the amount of treatment provided

Charting the data

Where available, data were extracted from each study regarding study characteristics, participant characteristics, intervention details, and dose parameters (Table 2). A second author (J.P.) double-rated 10% of studies for study design and outcome measure, reaching 91% consistency. A data charting template was created and populated by the first author. The template was modified iteratively to accommodate additional concepts as these were encountered in the literature.

Table 2 Data items extracted from selected studies

RESULTS

Literature search results

As per Figure 2, the literature search ultimately yielded a total of 104 intervention studies that reported the amount of therapy provided. A further eight articles meeting inclusion criteria were identified by searching bibliographies of the included studies. A total of 112 papers are included in this review (Appendix 1). A subgroup of 14 papers emerged which examined dose-response by comparing the administration of different amounts of the same intervention across groups or individuals (Appendix 2).
Study characteristics

Year of publication

Year of publication ranged from 1969 to 2019 (Figure 3). The year with the most published articles in this yield was 2018 (n = 14). The subgroup papers were published between 2005 and 2019.

Figure 3 Number of publications by year of publication

Sample size

In total, studies reported data from 2,128 individuals with post-stroke aphasia (median n = 8). Sixty-seven studies (60%) reported on 10 participants or fewer (Figure 4). Of these, 17 studies involved a single participant. Some individual participants with aphasia were included in more than one published paper. For example, Cherney provided a secondary analysis of data from a subgroup of participants previously reported in Lee and colleagues.44, 68, 69, 75, 76, 109

Figure 4 Number of publications by sample size

Time post-onset

Studies were categorised by the critical time points of recovery proposed by the Stroke Rehabilitation and Recovery Roundtable with one modification: early and late sub-acute epochs were combined as ‘subacute’. This reflects historic reporting of time post-onset in the aphasia literature and reporting within the included studies. All studies reported time post-onset. The vast majority of studies (n = 86) involved participants in the chronic phase of recovery (Figure 5). Five studies involved participants
Treatment dose in post-stroke aphasia

recruited during the acute phase and eight studies during the subacute phase. A number of studies included participants across multiple phases of recovery; acute to subacute (n = 4), subacute to chronic (n = 4), and acute to chronic (n = 5).

Figure 5 Number of publications by time post-onset and primary outcome

Reported outcome measures

Outcome measures were classified according to the International Classification of Functioning, Disability, and Health (ICF). In excess of 90 outcome measures were reported in this yield. The majority of papers in this review used a measure of impairment-level language function (Figure 5). A small number of papers reported activity- and participation-level communication measures. Very few studies reported measures of wellbeing, quality of life, or participant satisfaction.

Primary outcome measures

Seventy-nine percent of studies (n = 89) use at least one measure of language impairment (as demonstrated on standardised aphasia tests or non-standardised probes of linguistic functions) as the primary outcome measure, 18% of papers (n = 20) use measures of communication activity/participation via functional real-life use of language in connected speech, discourse analysis techniques, or communication rating scales, and 3% (n = 3) report both impairment and activity/participation measures as co-primary outcomes.

Secondary measures

Due to the substantial variability across the included studies, secondary measures will be described in terms of relative frequency. Studies in this review used omnibus aphasia
Treatment dose in post-stroke aphasia

batteries to classify aphasia type and severity. A large number of language function measures are reported. Many studies report use of customised measures of impairment, particularly naming batteries, tailored to suit specific participants and treatments. Frequently reported surrogate measures of functional communication skills include the Communicative Effectiveness Index\textsuperscript{149} and the Communicative Activity Log\textsuperscript{31}. A variety of non-linguistic measures used to determine presence and severity of comorbid cognitive dysfunction are reported, with the Raven’s Coloured Progressive Matrices\textsuperscript{150} by far the most frequently reported. Measures of quality of life (e.g., Stroke and Aphasia Quality of Life Scale – 39),\textsuperscript{151} well-being, and patient satisfaction (e.g., Communication Outcomes After STroke)\textsuperscript{152} are only occasionally reported. A small number of assessment tools used to identify concomitant motor-speech impairment are also reported.

Study design

A variety of study designs were retrieved (Figure 6). The majority of studies report single-subject methodologies as defined by the Risk of Bias in N-of-1 Trials (RoBiNT) scale.\textsuperscript{153} Aligned with the RoBiNT scale, we have differentiated between single-case experimental designs (SCED, n = 12) which can demonstrate cause-effect relationships between the intervention and changes in the target behaviour, and other single-subject methodologies including quasi-experimental single-case AB designs, and non-experimental pre-post designs and case studies (n = 64) which cannot unequivocally demonstrate treatment effect due to a lack of experimental control.\textsuperscript{153} Randomised controlled trials (RCT, n = 25) and non-
Treatment dose in post-stroke aphasia

randomised controlled trials (Non-RCT, n = 11) constitute approximately one third of the yield.

Figure 6 Number of studies by study design

Total doses reported in the yield

Unsurprisingly, the majority of studies in this yield report dose as the number of hours or sessions of treatment provided (Figure 7), or both. Approximately one quarter (27%) report therapeutic inputs, usually the number of times stimulus items were presented over the intervention period, or client acts, most commonly in the form of response accuracy. Three studies in this review report time-on-task, a measure of the time spent actively engaged in treatment during a session.

Figure 7 Number of studies reporting specific dose variables

It is difficult to get an accurate picture of how much treatment is provided in aphasia intervention studies due to inconsistent measurement and reporting of dose parameters. Many studies report the treatment schedule such that the prescribed dose can be calculated, but this is not always the case. Furthermore, the prescribed dose may differ to the actual dose that participants receive due to participants missing or refusing treatment sessions. The table in Appendix 1, therefore, lists the total dose that was either prescribed, actually provided, or estimated based on the treatment schedule reported in each study.

Prescribed hours of treatment ranged from one hour to 100 hours. The most frequently prescribed dose of 30 hours is reported in 16 studies (14%), reflective of the prevalence of treatment schedules that follow Pulvermuller and colleagues’ seminal CIAT
Treatment dose in post-stroke aphasia

Dose as a count of therapeutic elements may be incomparable across interventions due to probable differences in active ingredients of different therapies; however, the maximum reported dose in a lexical retrieval paradigm comes from Rieu and colleagues who provided 4,000 therapeutic inputs over 10 sessions in a cued naming protocol while Knollman-Porter and colleagues provided 8,400 therapeutic inputs to one participant over 20 sessions in a word-picture verification task designed to improve auditory comprehension.93, 126

Adjuvant treatments

In clinical aphasia research, adjuvant treatments are provided to participants with the goal of enhancing the effectiveness of the primary intervention. A number of approaches designed to stimulate aphasia recovery are reported in this yield including non-invasive (n = 4) and invasive brain stimulation (n = 1), pharmacology (n = 5), and physical exercise (n = 1). None of the studies reporting adjuvant treatments made comparisons between different doses of the primary behavioural intervention.

DISCUSSION

This scoping review yielded papers reporting on 50 years of post-stroke aphasia intervention. These studies comprise single-subject methodologies through to large-scale RCTs. Participants were most often in the chronic phase of recovery and interventions predominantly targeted impairment-level linguistic skills with fewer interventions specifically designed to improve communication activity and participation. A vast array of outcome measures was reported in this yield, consistent with previous reviews demonstrating a plethora of measures used in the aphasia literature.154 The results will now be discussed as they relate to the main research question addressed in this review.
Treatment dose in post-stroke aphasia

In the post-stroke aphasia literature, how is treatment dose conceptualised, measured and reported?

Dose conceptualisation

Researchers undertaking the studies in this review have conceptualised dose in one of two ways: either as a measure of the continuous variable time or as a count of discrete variables, i.e., therapeutic elements. Baker’s dose and intensity parameter model provides a framework which can be applied to post-stroke aphasia interventions.14

A potentially beneficial elaboration of Baker’s model of dose parameters would be to clarify the distinction between different dose variables. Figure 8 demonstrates that dose could be conceptualised as a specific element of a particular therapy (discrete variable), as a measure of time (continuous variable), or both. Well-defined interventions that target a particular language function, for example, semantic feature analysis (SFA), would be best served by measuring dose in terms of the number of therapeutic elements provided over the course of treatment (i.e., total dose [elements] = session dose [elements] x session frequency x total intervention duration). Alternatively, interventions that utilise multiple therapy approaches per session or social approach therapies where improved communicative exchanges are facilitated through strategy use and/or environmental enhancement (e.g., supported conversation training) may be best suited to quantifying total dose as a product of time (i.e., total dose [hours] = session dose [minutes] x session frequency x total intervention duration), unless the component tasks (e.g., SFA, conversational scripts, strategy-use training module tasks, etc) could be isolated, quantified, and tallied separately.
Treatment dose in post-stroke aphasia

Figure 8 Dose conceptualised as either a discrete variable or a continuous variable or both, based on Baker (2012)

It remains unclear whether the way in which dose is conceptualised has any effect on the interpretation of treatment effectiveness. Further examination and comparison of both discrete and continuous dose variables will promote greater understanding of how, and for whom, post-stroke aphasia interventions work.

Dose measurement and reporting

There is inconsistent measurement and reporting of dose in the aphasia intervention literature. The majority of these studies measure and report the total duration of treatment prescribed or provided while fewer studies report total dose as a sum of therapeutic elements (e.g., total number of therapeutic inputs provided or client acts performed). It is surprising that only three studies in this review report the more refined measure of time-on-task considering the relative ease with which computer-assisted or computer-delivered treatments could capture this measure. As previously stated, measuring total dose in hours eliminates the opportunity to examine responses to specific therapeutic elements, the active ingredients of intervention. Optimal delivery of active ingredients will enhance service delivery and patient outcomes. It is tempting therefore to home in on the therapeutic elements of complex behavioural interventions in order to examine and evaluate dose-response relationships. However, a number of issues regarding measurement and reporting of dose parameters prevail in the post-stroke aphasia literature.
Therapeutic elements are not routinely measured or reported

There have been many missed opportunities for capturing and reporting discrete therapeutic elements from small-scale single-subject designs to large RCTs. For example, the SP-I-R-IT study purported to be dose-controlled, in that both the intensive and regular groups received 100 hours of therapy. The authors acknowledge that, while participants did on average receive similar total dose hours, examination of discrete therapeutic elements would have allowed more fine-grained analysis of treatment effects. Additionally, in both research and clinical practice total treatment dose is frequently augmented through the provision of self-administered home-based therapy. Increasingly, the feasibility and effectiveness of self-directed computer- or tablet-based treatments is being explored. While prescribed treatment schedules are routinely reported in these studies, the reliability of participants’ compliance with practice schedules is rarely reported. As Kurland and colleagues note: “Future studies of the benefits of [home practice] should take advantage of technological advances in mobile health technology … that can allow for remote monitoring, video/audio collection of speech samples, reaction time, practice time, and remote adjustment of task difficulty.”

Discrete therapeutic elements are reported but not analysed

In this yield of studies, particularly those reporting naming interventions, the number of stimulus items, cues, accurate responses, inaccurate responses, and self-corrected responses are often reported. In addition to reporting the number of stimuli and protocolised cues used, there is an opportunity to examine the dose-response relationship for individual participant outcomes with regard to these therapeutic elements.

Furthermore, naming studies vary in the way that stimuli and naming attempts are balanced. For example, Fillingham and colleagues found that the number of naming attempts
correlates with picture naming accuracy, a finding replicated by DeDe and colleagues albeit under very different treatment conditions. However, Snell and colleagues found that the size of stimulus sets correlates with the number of words learned in therapy and that this correlation was not affected by aphasia severity. The optimal balance between the number of stimuli and the number of practice opportunities thus remains to be resolved. There are also unanswered questions regarding how stimulus items should be distributed within sessions to enhance learning of individual items. As Dignam and colleagues postulated, distributed practice may enhance new word learning and maintenance of treatment gains. The effect of spaced retrieval within individual treatment sessions needs to be systematically explored.

Current reporting guidelines (e.g., TIDieR) need to be extended to encourage systematic measurement and reporting of dose variables and treatment schedules. Routine analysis will contribute to the identification and exploration of key therapeutic elements and, thus, a deeper understanding of how, and for whom, behavioural interventions work.

Different doses across participants/groups are not analysed

The amount of therapy participants receive often deviates from the treatment protocol due to factors beyond experimental control (e.g., participant withdrawal, missed treatment sessions, etc). For example, Wenke and colleagues describe their pilot RCT in which participants received either four or eight hours per week of a comprehensive aphasia treatment program over eight weeks. The two groups received different total hours of treatment (i.e., 32 vs 64 hours); however, no formal between-group analyses of participant outcomes was performed due to unanticipated withdrawals, small sample size, and participant heterogeneity. Therefore, possible dose-response relationships were not examined. Likewise, the two groups examined by Rodriguez and colleagues received different doses but the groups were pooled.
Treatment dose in post-stroke aphasia

for analysis of treatment effects, thereby obscuring possible between-group dose-related differences.

In summary, dose has been conceptualised as both a discrete variable and a continuous variable in aphasia interventions. The measurement and reporting of dose parameters is inconsistent across the post-stroke aphasia intervention literature. A model for conceptualising and measuring dose parameters exists, yet has not been routinely employed in the reporting of results. Reporting guidelines should be extended to encourage researchers to provide more detail regarding treatment dose parameters. More consistent measurement and reporting will allow for more rigorous synthesis of findings and comparison between different interventions which may lead to increased treatment effectiveness and efficiency and, ultimately, better outcomes for people recovering from post-stroke aphasia.

Additional emerging factor: Therapy studies may be under-dosed

A common refrain in the aphasia literature is that interventions are often administered at doses too low to stimulate the neural reorganisation thought to underlie behaviour change. It is open to conjecture just how far below optimal dose current therapy regimes are. The idea of dose ranging, where doses are escalated until the point at which the side-effects of intervention outweigh the benefits of participation, may be new to behavioural interventions in stroke rehabilitation. There are no published reports of dose ranging studies in aphasia. While some studies in this review report doses of up to 100 hours and 108 sessions, such high doses are uncommon. The current clinical reality is that 100 hours of treatment is rarely feasible due to costs and logistics, and may not be tolerable or agreeable to many people with aphasia. High dose of therapeutic elements need not equate to prolonged intervention periods.

An obvious solution is to increase session dose of the active ingredients of therapy. There is
Treatment dose in post-stroke aphasia

preliminary evidence to suggest that gains in language and communication functions can be achieved with relatively brief interventions. For example, picture naming accuracy and discourse-level word retrieval can improve to statistically significant levels and be maintained after just one treatment session for some people with aphasia.\textsuperscript{55, 81}

Additional emerging factor: Intervention tolerance

A balance between the effort required to engage in treatment and the potential reward of improved language and communication skills needs to be negotiated on a person-by-person basis. Treatment schedules that provide large amounts of therapy over a long duration may not be tolerable or even preferable for all people with aphasia.

Person-level factors that influence intervention tolerance and expectations of recovery need to be considered.\textsuperscript{17} For example, tolerance may be mediated by time post-onset, concurrent medical and cognitive comorbidities, fatigue, psychosocial and interpersonal factors, adjustment and grief associated with change of identity and loss of function, and personality traits.\textsuperscript{117} Signs that a person is not tolerating treatment may include withdrawal or refusal to receive treatment,\textsuperscript{12} degraded performance of an established skill due to “reactive impedance” (i.e., boredom, mental fatigue, inattention, and deficient processing),\textsuperscript{157} or reduced patient satisfaction with treatment.\textsuperscript{93}

Treatment-related variables such as difficulty of therapy tasks, and the dose and intensity of treatment schedules may also impact tolerance. Time constraints affecting access to clinical services and costs associated with prolonged treatment necessitate the development of efficient models of care. Furthermore, expediated recovery to acceptable levels of function may allow people with aphasia to return to preferred activities sooner with obvious implications for enhanced well-being.
Treatment dose in post-stroke aphasia

There were no attempts to determine the maximum tolerable dose of any aphasia intervention in the studies included in this review. Signals are emerging from the acute and subacute periods that total doses in excess of 60 hours may not be tolerable for people during this phase of recovery from stroke.\textsuperscript{43, 49} In the chronic phase, an upper limit has not been established for high dose, high frequency interventions, including those that provide very high session dose.\textsuperscript{81, 126} There is evidence in the literature of selective exclusion of participants from clinical trials due to a predicted inability to tolerate prescribed interventions; however little or no discussion of the predictive determinants driving these decisions is reported.\textsuperscript{25} Further exploration of the person- and treatment-specific factors likely to impact intervention tolerance is required. Clear delineation of these factors will enable enhanced treatment prescription and individual recovery from post-stroke aphasia.

Future directions for research on post-stroke aphasia treatment

Synthesis of findings from dose comparison studies

Fourteen papers in this yield explored dose-response relationships by comparing groups or individuals who received different amounts of the same therapy throughout a prescribed intervention period, with mixed findings (Appendix 2). Few studies set out to systematically compare dose-response relationships; rather, the majority performed exploratory post-hoc statistical analysis after finding participants received different doses throughout the treatment schedule. However, future synthesis of the findings from these reports, where possible, may reveal important signals regarding dose-response relationships in post-stroke aphasia interventions.
Consensus definitions for dose parameters in aphasia interventions are required

Inconsistent measurement and reporting of dose parameters across the aphasia literature stems from a lack of standard definitions. The terminology in the existing model provided by Baker lays the foundation for discussions regarding dose and intensity parameters.\textsuperscript{14}

Consistent use of terminology will have important implications for the development, implementation, and evaluation of dose and intensity studies, for synthesis of data across these studies, for the theoretical exploration of what drives treatment response in these interventions, for clinical decision-making regarding service delivery, and for health policy makers. Once consensus definitions are in place, reporting guidelines (e.g., TIDieR) need to be extended to encourage systematic routine measurement and reporting of dose variables and treatment schedules.

Dose ranging and maximum tolerable dose

Upper limits of dose have yet to be established across the post-stroke recovery continuum. There is a pressing need to determine upper dose limits of aphasia interventions through incremental escalation studies across the critical timepoints of recovery following stroke. The amount of time and effort expended to achieve a clinically significant and worthwhile change in language skills or communication function requires close consultation with participants to determine the criteria by which to define optimal treatment outcome. Future intervention studies should drive improved language and communication outcomes in post-stroke aphasia through systematic dose ranging studies across a range of aphasia interventions. A number of treatment approaches, particularly those targeting lexical retrieval, are ready for this level of exploration.
**Limitations**

The question at the base of this review is broad, in line with scoping review methodology. However, it is acknowledged that the studies included for review represent a small subset of the aphasia intervention literature. Lack of consensus on terminology and dose parameter reporting standards may also mean that some relevant studies may have been missed. This review did not attempt to systematically evaluate the quality of the evidence due to the large yield and limited resources available to perform this task, nor was the data extraction chart checked for accuracy by a second reviewer.

The final major limitation is that treatment dose is invariably confounded with treatment *intensity*. In the aphasia literature, intensity has come to be synonymous with *frequency* and means the rate at which a particular dose is provided: it is the quotient of dose over time. Dose and intensity are, therefore, interdependent. When evaluating interventions, we are faced with the issue of determining which parameter, if any, confers the treatment effect. It is possible, perhaps probable, that the overall impact on outcome is a result of the interaction between a number of these variables. Further research is required to compare and contrast the relative effects of treatment dose and treatment intensity.

**CONCLUSION**

Treatment dose is an important parameter of post-stroke aphasia interventions. Most aphasia intervention studies report the total number of treatment hours or sessions provided rather than counts of therapeutic elements. A conceptual framework for describing and reporting discrete therapeutic elements exists and, with sufficient uptake, will improve consistency of measurement and reporting across aphasia treatment trials. At present, inconsistent measurement and reporting of dose may hamper systematic synthesis of findings across intervention studies. Nevertheless, there is emerging evidence of dose-response relationships.
in a small number of studies. However, studies employ a wide variety of treatment schedules (i.e., session dose, session frequency, and intervention duration) and the particular combination of these may also impinge on the relationship between efficacy and total dose.

High dose interventions delivered over short intervention periods may improve treatment efficiency. Person- and treatment-level factors that mediate tolerance of high dose interventions require further investigation. Further systematic exploration of dose-response relationships in post-stroke aphasia treatment is required.

Funding

This work was supported by an Australian Government Research Training Program Scholarship and the NHMRC funded Centre for Research Excellence in Aphasia Recovery and Rehabilitation (#1153236).
Treatment dose in post-stroke aphasia

Bibliography


<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Title</th>
<th>Journal/Journal Volume</th>
<th>Pages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brady, M., et al.</td>
<td>2016</td>
<td>Speech and Language Therapy (SLT) for aphasia after stroke: cochrane systematic review evidence of therapy regimens, delivery models and theoretical approaches.</td>
<td><em>European stroke journal</em>, 1(1):</td>
<td>693-</td>
</tr>
</tbody>
</table>
### Treatment dose in post-stroke aphasia

<table>
<thead>
<tr>
<th>No.</th>
<th>Reference</th>
</tr>
</thead>
</table>
Treatment dose in post-stroke aphasia


Treatment dose in post-stroke aphasia


Treatment dose in post-stroke aphasia


Treatment dose in post-stroke aphasia


Treatment dose in post-stroke aphasia


<table>
<thead>
<tr>
<th>Page</th>
<th>Treatment dose in post-stroke aphasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>840</td>
<td></td>
</tr>
<tr>
<td>841</td>
<td></td>
</tr>
<tr>
<td>844</td>
<td></td>
</tr>
<tr>
<td>847</td>
<td></td>
</tr>
<tr>
<td>848</td>
<td></td>
</tr>
<tr>
<td>850</td>
<td></td>
</tr>
<tr>
<td>851</td>
<td></td>
</tr>
<tr>
<td>853</td>
<td></td>
</tr>
<tr>
<td>855</td>
<td></td>
</tr>
<tr>
<td>856</td>
<td></td>
</tr>
<tr>
<td>858</td>
<td></td>
</tr>
<tr>
<td>859</td>
<td></td>
</tr>
<tr>
<td>861</td>
<td></td>
</tr>
<tr>
<td>862</td>
<td></td>
</tr>
</tbody>
</table>
Treatment dose in post-stroke aphasia


Treatment dose in post-stroke aphasia


Treatment dose in post-stroke aphasia


Treatment dose in post-stroke aphasia


Treatment dose in post-stroke aphasia


Treatment dose in post-stroke aphasia


Treatment dose in post-stroke aphasia


Treatment dose in post-stroke aphasia


Treatment dose in post-stroke aphasia


Treatment dose in post-stroke aphasia

1067 Figure and table legend
1068 Figure 1 Model of dose and intensity parameters involved in determining optimal intervention intensity (Baker, 2012 based on Warren et al., 2007)
1070 Table 1 Search terms relating to treatment dose in aphasia
1071 Figure 2 PRISMA flow diagram showing the study selection process
1072 Table 2 Data items extracted from selected studies
1073 Figure 3 Number of publications by year of publication
1074 Figure 4 Number of publications by sample size
1075 Figure 5 Number of publications by time post-onset and primary outcome
1076 Figure 6 Number of studies by study design
1077 Figure 7 Number of studies reporting specific dose variables
1078 Figure 8 Dose conceptualised as either a discrete variable or a continuous variable or both, based on Baker (2012)