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Mediators, confounders and effectiveness of interventions for medication adherence after stroke.

Commentary on:

- **Al AlShaikh S, Quinn T, Dunn W, Walters M, Dawson J. Predictive factors of non-adherence to secondary preventative medication after stroke or transient ischaemic attack: A systematic review and meta-analyses. Eur Stroke J. 2016;1(2):65-75.**
- **Bridgwood B, Lager KE, Mistri AK, Khunti K, Wilson AD, Modi P. Interventions for improving modifiable risk factor control in the secondary prevention of stroke. The Cochrane database of systematic reviews. 2018;5:Cd009103.**
- **Gibson JME, Miller C, Coupe J, Jones SP. Medication-taking after stroke: a qualitative meta-synthesis of the perspectives of stroke survivors, informal carers and health professionals. Fam Pract. 2020;37(1):4-**

KEY POINTS

- Patients who present with an existing disability, reduced cognitive function, take multiple medications, have a poor quality of life, and have had a previous stroke are associated with reduced medication adherence.
- There is evidence that trust and belief in the medication are important modifiable factors which are linked to positive medication adherence.
- There is some evidence that education may be effective for improving medication adherence.

Background to the reviews

There are 13.7 million new stroke cases globally per year, with a total of 80.1 million stroke survivors (GBD 2019). It is the second most common cause of death in the world and is attributed to 6.17 million deaths per year (GBD 2018). Around one in four people can expect to have a stroke within their lifetime (Feigin et al. 2017). The consequences of stroke can include reduced mobility (Michael et al. 2005), limb weakness, spasticity, pain, psychosocial issues, language difficulties (Norrving and Kissela 2013) and reduced quality of life (Bays 2001).

After a stroke or a transient ischaemic attack [TIA] people have a substantial long-term risk of recurrent stroke (van Wijk et al. 2005; Dhamoon et al. 2006; Feng et al. 2010; Edwards et al. 2017). Secondary prevention medication is an important (Kikuchi et al. 2012; Hankey 2014) and effective strategy to reduce the risk of stroke recurrence (Toyoda 2009; Hill and Hare 2019). However, medication adherence and medication persistence rates are low after stroke (Zhang et al. 2019). It is

important to understand stroke survivors' and carers' experiences of medication-taking after stroke, barriers and facilitators of medication adherence, and the effectiveness of interventions to improve them in order to provide effective support.

This commentary aims to critically appraise the methods used within three systematic reviews exploring medication adherence after stroke (AlShaikh et al 2016, Bridgwood et al 2018, Gibson et al 2020) and to synthesise the findings in the context of clinical practice.

Methods and Quality of the reviews

Selection of reviews was based on relevance to the broader issues surrounding medication adherence in a stoke population, rather than focussing on one moderating factor, e.g. the association with cognitive impairment. Additionally, they were the most recent reviews in this area.

The three reviews focused on specific populations of stroke survivors (Al AlShaikh et al. 2016; Bridgwood et al. 2018; Gibson et al. 2020) and informal primary and secondary care (Gibson et al. 2020). They used qualitative and quantitative review techniques to explore three key aspects of medication adherence:

1. Quantitative - Meta-analysis: What are the **important moderating factors** in relation to medication non-adherence after stroke? (Al AlShaikh et al. 2016).
2. Qualitative - Meta-ethnography: What are the **views and lived experiences** of community-dwelling stroke survivors, caregivers and health care professionals related to medication taking? (Gibson et al. 2020).
3. Quantitative - Meta-analysis: What interventions are **effective** in improving medication taking? (Bridgwood et al. 2018).

Outcomes for the reviews explored views, experiences, beliefs, strategies, solutions, factors which influence adherence, and adherence itself. Using the PICO tool (Schardt et al. 2007) as an organising framework, components of clinical evidence were compared for each review (see Table 1).

Table 1: PICO of AlShaikh et al 2016, Gibson et al 2019 and Bridgwood et al 2018

PICO	(AlShaikh et al 2016)	(Gibson et al 2019)	(Bridgwood et al 2018)
Population	Adults who have suffered a stroke	Community-dwelling stroke or TIA survivors, informal carers, primary or secondary care HCPs who prescribe medication-taking after TIA or stroke	Adults with a confirmed diagnosis of ischaemic stroke, haemorrhagic stroke, or TIA
Exposure/ **I**ntervention	Prescribed medication for the prevention of recurrent cardiovascular events	Being prescribed or being involved in the prescription of medication	Interventions which aimed to improve modifiable risk factor control through increased adherence
Control	Not applicable	Not applicable	Yes: Usual care
Outcomes	Factor(s) that influenced medication adherence.	Lived experiences, views and beliefs, strategies and solutions.	Patient outcomes such as body mass index, blood pressure, and any indicator of patient adherence

Study type	No study type specified.	Qualitative studies and mixed methods	Randomised controlled trials, parallel group trials, cluster-randomised trials and cross-over trials

Using a modified Joanna Briggs Institute Critical Appraisal tool for systematic reviews (Joanna Briggs Institute 2017), it was judged that the systematic reviews by Gibson et al 2020 and Bridgwood et al 2018 used appropriate methods for all 11 criteria (See Table 2 for full list of criteria and corresponding methods) and provided an accurate summary of the results of the included studies. The other systematic review (AlShaikh et al 2016) used appropriate methods for only 9 of 11 criteria. The screening methods were not appropriate, as although the first stage of dual independent title screening was appropriate (Mateen 2013; Rathbone et al. 2017), the second stage of single reviewer full paper screening was not (Buscemi et al. 2006; Waffenschmidt et al. 2019). The review also lacked a description of the data extraction methods used. Both of these issues can lead to errors and exclusion of eligible studies, but overall AlShaikh et al (2016) probably provides an accurate summary of the results of the available studies.

Table 2: Quality assessment and methods of AlShaikh et al 2016, Gibson et al 2019 and Bridgwood et al 2018 (Quality assessment of the systematic reviews was carried out by JH and JH).

Criteria	(AlShaikh et al 2016)	(Gibson et al 2019)	(Bridgwood et al 2018)
1. Is the review question clearly and explicitly stated?	Yes: The aim of this review was to identify factors associated with non-adherence after stroke.	Yes: The aim of this review was to undertake a meta-synthesis of qualitative studies of medication-taking after stroke. With a focus on lived experiences, views and beliefs, strategies and solutions.	Yes: To assess the effects of stroke service interventions for implementing secondary stroke prevention strategies on modifiable risk factor control.
2. Were the inclusion criteria appropriate for the review question?	Yes: See Table 1 for full PICO criteria.	Yes: See Table 1 for full PICO criteria.	Yes: See Table 1 for full PICO criteria.
3. Was the search strategy appropriate?	Yes: A robust multi-database search was undertaken.	Yes: A robust multi-database search was undertaken and snowball sampling.	Yes: A robust multi-database search was undertaken and snowball sampling.
4. Were the sources and resources used to screen studies adequate?	No: The first stage of screening used two reviewers independently reviewing titles only. Full paper screening was done by single reviewer.	Yes: Title and full paper screening was carried out by two independent reviewers	Yes: Title and full paper screening was carried out by two independent reviewers
5.Were the	Yes: Pre-specified tool	Yes: The use of Walsh	Yes: All included studies

criteria for appraising studies appropriate?	based upon Newcastle–Ottawa Scales (Wells 2019) and Cochrane Library tool for assessing risk of bias was used (Higgins et al. 2011).	and Downe's criteria was used to assess the quality of the included studies.	were assessed using the Cochrane risk of bias tool (Higgins et al. 2011)
6.Was critical appraisal conducted by two or more reviewers independently?	Yes: Two independent reviewers critically appraised all included studies	Yes: Two independent reviewers critically appraised all included studies	Yes: Three independent reviewers critically appraised all included studies
7.Were there methods to minimize errors in data extraction?	No: No description of whether data extraction was carried out independently and duplicated.	Yes: Data extraction was carried out by two independent reviewers using a bespoke pre-piloted data extraction form.	Yes: Data extraction was carried out by two independent reviewers using a pre-specified data extraction form
8.Were the methods used to combine studies appropriate?	Yes: A random effects model was used.	Yes: The use of the meta-synthesis technique by Noblit and Hare was used (Noblit 1988).	Yes: A random effects model was used for each prespecified intervention category; subgroup analysis was carried out for patient age, condition type, stroke severity and specific risk factor management strategy
9.Was the likelihood of publication bias assessed?	N/A: Less than 10 studies (Higgins et al. 2011).	N/A	Yes: Only visual inspection of funnel plots.
10.Were recommendations for policy and/or practice supported by the reported data?	Yes: Full findings and implications to practice will be discussed below.	Yes: Full findings and implications to practice will be discussed below.	Yes: Full findings and implications to practice will be discussed below.
11.Were the specific directives for new research appropriate?	Yes: Recommendation that further research is required around which interventions are effective in improving treatment adherence.	Yes: Particular areas of lack of research were identified in studies in low to moderate income countries, acute post stroke and carers and healthcare professional's perception of medication adherence.	Yes: Appropriate recommendations were made based on the findings of the study
Total criteria achieved/not	8/11	11/ 11	11/11

applicable			

Quality of studies included in the reviews

The systematic review by AlShaikh et al (2016) identified that the majority of studies had a high risk of bias: often, outcome assessors were non-blinded and most studies used only self-reporting of adherence. The qualitative systematic review by Gibson et al (2019) identified that the majority of studies included were of medium quality. Quality issues included lack of an appropriate theoretical framework, data saturation, participant validation, and reporting of important patient data. There were also some ethical concerns. The review by Bridgwood et al (2018) classified the evidence for the outcome of adherence to be of low-quality using GRADE (Kavanagh, 2009), because the studies included were heterogeneous, had high risk of bias and findings were inconsistent across the studies. The authors concluded that the true effect might be markedly different from the estimated effect (Bridgwood et al 2018) See Table 3 for summarisation of quality of included studies.

Table 3: Quality of studies included in the reviews.

	AlShaikh et al (2016)	**Gibson et al (2020)**	**Bridgwood et al (2018)**
Critical appraisal tool used for summary statement of quality	Scales (Wells 2019) and Cochrane Library tool (Higgins et al. 2011)	Walsh and Downe's criteria (Walsh and Downe 2006)	GRADE (Kavanagh, 2009)
Quality score	Out of the 29 included studies 27 were deemed to be of high risk and 2 were low.	Of the 12 included studies 9 were deemed to be of moderate quality and 3 were deemed to be of weak quality	The outcome of medication adherence was downgraded due to heterogeneity, high risk of bias and inconsistency
Descriptive term:	High risk of bias (study level assessment of risk of bias)	"Medium quality" (study level assessment of quality)	Low quality evidence

Findings

Important factors - Medication non-adherence

AlShaikh (2016) identified predictive factors of non-adherence to secondary preventive medication after stroke/TIA. The review included 16 studies and 69,137 patients. All included studies provided a measure of medication non-adherence, ranging from 11.3% to 45.2%. Meta-analysis showed that overall, nearly a third (30.9%) of participants did not adhere to preventative medication.

The authors reported their data according to the World Health Organization (WHO) classification of predictive factors of non-adherence: patient-related, social and economic, therapy-related, health

system or health care team, and condition (stroke)-related factors (World Health Organisation 2003). The most commonly reported factors which related to increased medication adherence were patients who have a positive belief in the medication, the presence of a carer or living in a care home, understanding of the medication rationale and having previous treatment by the same medication class respectively. The most commonly reported factors which related to reduced medication adherence were patients who have a disability

reduced cognitive function, number and frequency of prescribed drugs, more severe stroke and concerns about their medication. See Table 4 most frequently reported medication adherence factors.

Table 4: Medication adherence associated factors

World Health Organization (WHO) classification	Patient related factors	Number of studies which reported the factor to be significant	Positively or negatively associated
Patient related factors	Patients who reported with concerns about their medication	4	Negatively
	Patients had a positive belief in the medication	4	Positively
Socioeconomic factors	Presence of a carer or living at home rather than in institutional care	4	Positively
	Having some sort of education	2	Positively
Therapy-related factors	Disability	6	Negatively
	Reduced cognitive function	4	Negatively
	Poor quality of life	3	Negatively
	Low mood	2	Negatively
	Smoking	2	Negatively
	Alcohol consumption	2	Negatively
Prescribed regimen factors	Understanding of medication rationale	4	Positively
	Previous treatment by the same medication class	3	Positively
	Cost of medication	3	Negatively
	Number and frequency of prescribed drugs	4	Negatively
Health system or health care team factors	Treated in stroke unit	2	Positively
	Medical insurance	2	Positively
	Accessible health care facility	2	Positively
Stroke-related factors	More severe stroke	4	Negatively
	Previous stroke incidence	3	Negatively
	Symptoms of post-traumatic stress disorder	2	Negatively

Four factors were eligible for meta-analysis: absent history of atrial fibrillation, disability, polypharmacy and age of the patient, but no significant associations with medication adherence were found.

The review authors noted that much of the available literature was based on patient or drug factors, but institution or healthcare factors should not be forgotten. They suggest that clinicians could reduce the burden of treatment on patients by communicating the barriers of adherence and identifying factors that could be reversed such as mis-beliefs or complex regimens. The authors imply that it is important to identify interventions that can detect difficulties for medication administration and effectively support patients to adhere to secondary preventative medication.

Views and lived experiences related to medication taking

Gibson et al. (2020) explore the views and lived experiences of taking medicine after stroke from the perspective of community-dwelling stroke survivors, informal carers, and healthcare professionals. The review identified 12 studies including 412 participants, of which two thirds were stroke survivors between 1 month to 20 years post-stroke.

Two overall themes were developed: 'doing medicines work' (all the work that goes into taking medications) and 'trust' (having trust in the medicines' efficacy and beliefs about healthcare). The theme of 'doing medicines work' included several types of work: information work, healthcare work, carer work, emotional work, and practical work, which were classified as sub-themes.

'Information work' focussed on the work patients do to understand and process the information about their medication such as why they are taking it and how to take it. Healthcare professionals are often the ones to provide this information and stroke survivors reported both positive and negative interactions in this respect. With healthcare professionals taking the time to explain the medications and answering questions to be a positive example of information work. However, it was felt that this positive experience was inconsistently delivered and there was a need for medication information to be provided long-term.

The sub-theme of 'healthcare work' provided further insight into how patients engage with healthcare services to obtain their medication, including monitoring and medicines reviews. Positive aspects included healthcare professionals being responsive to patients' medication concerns and difficulties. Negative aspects included patients' dislike of monitoring/review and the perceived negative consequence of additional medication being prescribed.

'Carer work' included support given by family members, friends, or neighbours to obtain, organize or supervise medication for the stroke survivor. It was acknowledged that this could cause conflict in the relationship and give rise to difficulties if the carer were not available.

'Emotional work' described the thoughts and feelings of stroke survivors as to why they need to take medication, primarily to avoid having another stroke. This was seen by healthcare professionals as a key motivator for medication adherence. Within this theme it was also noted that some stroke survivors had concerns about or disliked taking medication due to, for example, potential side-effects and stigma.

'Practical work' included the necessary activity required for a stroke survivor to take their medication such as storing and keeping track of doses, often relying on interaction with carers. Successful medication adherence required maintenance of a stable routine. In contrast a complex routine or one that required modification acted as a barrier to medication adherence.

The second main theme in this review was 'trust'. This relates to stroke survivors' and carers' belief in the efficacy of the prescribed medication. This could be hampered by the lack of obvious immediate benefit, but if there was a visible end point such as blood pressure reduction, this enhanced their trust in the efficacy of the medication. Furthermore, taking medication was mediated by a mutual trust between patients, carers and healthcare professionals.

The authors conclude that the substantial work required in 'medicines work' and the need for 'trust' in both the medicines and healthcare service 'are likely to constitute a substantial treatment burden regardless of the severity of the stroke'. In order to address this burden, the authors propose that healthcare professionals need to offer a clear information exchange with stroke survivors, reducing the amount of work involved for patients in accessing medication support, develop individualised strategies to address practical problems, help carers to support and ensure that patient concerns about medication and recurrent stroke are addressed.

What is effective in improving medication taking after stroke?

The Cochrane review by Bridgwood et al. (2018) synthesised studies of interventions for improving modifiable risk factor control in secondary prevention of stroke. The authors identified 42 random controlled trials [RCTs] with 33,840 participants, mostly in primary care or community settings. Twenty-six studies evaluated organisational interventions (changing how the healthcare service is provided) and 16 evaluated educational or behavioural interventions for participants. Most interventions lasted between three and twelve months with follow up from three months to three years. For most of the interventions, the comparator was standard care (30 RCTs). The remaining studies used active control comparators (4 RCTs) or provided educational but not individualised advice (7 RCTs). One study asked the control group to record stroke consultations/adverse events.

Organisational interventions consisted of those that formed part of a broader rehabilitation programme post-stroke (7 RCTs) and those that targeted secondary prevention (19 RCTs). Eight of these RCTs included a measure of adherence to secondary preventative medications. There was moderate quality evidence that organisational interventions resulted in improved outcomes for blood pressure target achievement compared to usual care (89 more per 1000 achieving their target, 95%CI: 21 more to 159 more). The eight RCTs which included a measure of adherence were not pooled due to substantial heterogeneity in the methods used. The majority of RCTs [low quality evidence] did not find a statistically significant difference for organisational interventions compared to control. The two RCTs which found a statistically significant difference in medication adherence included lifestyle counselling and blood pressure monitoring (Hornnes 2010; McAlister 2014).

Educational/behavioural interventions largely focussed on modifiable risk factors for stroke (11 RCTs). The remaining interventions delivered education on secondary stroke prevention as part of broader stroke education programmes (5 RCTs). Thirteen of these studies included a measure of adherence to secondary preventative medications. Data could not be pooled due to methodological heterogeneity. The majority of RCTs [low quality evidence] did not find a statistically significant difference for educational/behavioural interventions compared to control. All three studies which demonstrated a statistically significant difference compared to control included education

specifically focused on medication adherence (O'Carroll 2011; Peng 2014; Wan 2016). Two of the RCTs included specific goal setting around improving medication adherence routines (O'Carroll 2011; Wan 2016).

Within the wider review, the authors found no clear evidence that organisational interventions can improve modifiable risk factors or reduce incidence of cardiovascular events. In addition, educational interventions alone are unlikely to bring improvements without additional organisational change. They also noted that interventions which were associated with improved outcomes for secondary prevention, usually involved multidisciplinary team working. Medication adherence could therefore be improved through reinforcement of information by different team members.

Application to practice

Patients who present with an existing disability, reduced cognitive function, take multiple medications, have a poor quality of life, and have had a previous stroke are associated with reduced medication adherence. Subsequently these groups should be seen as a priority for screening and treatment.

There is evidence that trust and belief in the medication are important modifiable factors which are linked to positive medication adherence. Thus, it is important to ensure that the patient has trust and belief in the effectiveness of the medications being prescribed. This concept of trust has also been identified as an important moderating factor for the mutual trust between patient, carers, and healthcare workers and should be seen as a vital component of effective medication adherence interventions.

It is important that patients are provided with information about why the medication is given. This medication information should be clear, easy to access, continuous, responsive, individualised, and accessible for both patients and healthcare workers. The information given to the patient about their medication should be given in a timely manner and opportunities should be given to the patient to voice any concerns/questions they may have. When designing the medication strategy, the regularity of the routine should be considered, as lack of consistency may cause worsened medication adherence. As part of this educational strategy the use of goal setting and outcome monitoring such as blood pressure should be considered.

Keywords

Stroke, medication taking, medication adherence, predictive factors, education

CPD reflective questions

- Which out of the factors identified, which were associated with medication adherence, are modifiable?
- If you are designing an educational strategy for medication adherence what key factors should be included?
- Can any of the strategies identified within this paper be applied to your own area of practice?

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