Hospital Admissions Associated with Medication Non-adherence: A Systematic Review of Prospective Observational Studies

Supplementary

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eTable 1. Original Crombie tool and the operationalized domains of the Crombie tool used in this systematic review

An original domain of Crombie's tool	Operationalization of Crombie's tool
Appropriateness of design to meet the aims	1. Were the objectives/aims of the study clearly stated? 2. Was the design appropriate to meet the aims?
Adequate description of the data	3. Was the data described adequately in terms of method of participant selection, location, and time period?
Adequate representativeness of the sample to total	4. If a sample was used, the sample was representative of the total study population?
Adequate description of statistical methods	5. Did the authors describe adequately the statistical methods used?
Assessment of statistical significance	6. If appropriate, is it clear what was used to determine statistical significant (e.g. p value, CI)?
Clearly stated aims and likelihood of reliable and valid measurements	7. Was the tool/method used to measure medication non-adherence practical? 8. Was causal relationship assessed? Have they been evaluated by a reliable method/tool?
Report the response rates	9. Did the authors report the response rate? Was the information about non-responders stated?

eTable 2. Final quality assessment of the included studies using the amended Crombie tool
Each assessment item is "Yes (1 point)", "Unclear (0.5 point)", or "No (0 point)".

Domain	*McKenny, et al. (1976)*	*Stewart, et al. (1980)*	*Bergman, et al. (1981)*	*Yosselson-Superstine et al. (1982)*	*Bigby, et al. (1987)*	*Davidsen, et al. (1988)*	*Grymonpre, et al. (1988)*	*Col, et al. (1990)*	*Stanton, et al. (1994)*	*Courtman, et al. (1995)*	*Dartnell, et al. (1996)*	*Nelson, et al. (1996)*	*Murad, et al. (1997)*	*Malhotra, et al. (2001)*	*Chan, et al. (2001)*	*Martin, et al. (2002)*	*Otero Lopez, et al. (2006)*	*Samoy, et al. (2006)*	*Kongkaew. (2009)*	*Singh, et al. (2011)*	*Al-Arifi, et al. (2014)*	*Kongkaew, et al. (2015)*	*Gustafsson, et al. (2016)*	*Jolivot, et al. (2016)*	*Agreement (Value of Kappa)*
1. Were the objectives/aims of the study clearly stated?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	1.00
2. Was the design appropriate to meet the aims?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	1.00
3. Was the data describe adequately in terms of method of participant selection, location, and time period?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	1.00
4. If a sample was used, the sample was representative of the total study population?	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	U	Y	0.78
5. Did the authors describe adequately the statistical methods used?	N	N	Y	N	Y	N	Y	Y	Y	Y	N	Y	N	N	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	0.83
6. If appropriate, is it clear what was used to determine statistical significant (e.g. p value, CI)?	N	N	U	N	N	N	Y	Y	U	Y	N	U	N	U	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	0.93
7. Was the tool/method used to measure medication non-adherence practical?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	1.00
8. Was causal relationship assessed? Have they been evaluated with a reliable method/tool?	N	N	Y	N	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	Y	Y	Y	Y	N	N	Y	Y	N	0.90
9. Did the authors report the response rate? Was the information about non-responders stated?	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	N	N	Y	Y	1.00
Overall summary score	**6**	**6**	**8.5**	**4.5**	**8**	**7**	**9**	**9**	**8.5**	**8**	**7**	**8.5**	**5.5**	**7.5**	**9**	**9**	**9**	**9**	**8**	**8**	**4**	**8**	**8.5**	**8**	**0.75**
Risk of bias judgement	**M**	**M**	**L**	**M**	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**M**	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**M**	**L**	**L**	**L**	**1.00**

Abbreviations: Y=Yes, N=No, U=Unclear, M=moderate risk of bias, L=low risk of bias

eTable 3. Definition of preventability

Author (Year)	Definition of preventability
McKenny, et al. (1976)	NA
Stewart, et al. (1980)	NA
Bergman U, et al. (1981)	NA
Yosselson-Superstine, et al.(1982)	NA
Bigby J, et al. (1987)	NR
Davidsen, et al. (1988)	NA
Grymonpre, et al. (1988)	NA
Col N, et al. (1990)	NA
Stanton et al. (1994)	NA
Courtman BJ, et al. (1995)	The drug treatment was inappropriate , contraindicated, no measures were taken to counteract known effects of the drug, or the patient was noncompliant or insufficiently educated about medications
Dartnell JG, et al. (1996)	The likelihood that the admission could have been avoided if appropriate measures had been avoided if appropriate measures had been taken by health workers.
Nelson KM, et al. (1996)	Patient (1) did not take a drug that is known to reduce or prevent symptoms according to the prescribed directions, (2) had a known allergy, (3) had a disease for which the drug was contraindicated, and (4) took a drug that was not indicated, and possibly avoidable if there is a failure to monitor by a physician at reasonable time intervals and inadequate monitoring due to inability to see a physician (e.g., financial difficulties)
Murad, et al. (1997)	NA
Malhotra, et al. (2001)	NA
Chan M, et al. (2001)	A result of a drug-treatment procedure inconsistent with present-day knowledge of good medical practice or was unrealistic, taking the known circumstances into account.
Martin MT, et al. (2002)	NR
Otero Lopez MJ, et al. (2006)	NR
Samoy LJ, et al. (2006)	Event was defined as preventable if treatment was inconsistent with current knowledge of ideal medical practice including inappropriate drug, dosage, or route of administration relative to the patient's clinical condition, age, weight, and renal function; known drug allergy or previous reaction to drug; known drug interaction; noncompliance; laboratory monitoring not performed; and prescribing, dispensing, or administration errors.
Kongkaew C. (2009)	(1) Drug-related morbidity (DRM) preceded by a recognisable drug therapy problem (DRP). (2) Given the DRP, the DRM would have been reasonably foreseeable. (3) The cause of DRM would have been identifiable with reasonable probability (Hallas criteria probable or definite for causality).

Author (Year)	Definition of preventability
	(4) The cause of the DRM could have been reasonably controllable within the context and objectives of treatment. All four criteria must be fulfilled to confirm preventability
Singh H, et al. (2011)	Event was defined as preventable if drug treatment or lack thereof, was inconsistent with current best practice. Such inconsistencies included inappropriate drug, dosage, route or frequency for the patients clinical condition, age, weight or renal function, known drug allergy or previous reaction to drug; known drug interaction, non-adherence, lack of laboratory monitoring and prescribing, dispensing or administration errors.
Al-Arifi M, et al. (2014)	Patient (1) did not take a drug that is known to reduce or prevent the symptoms according to the prescribed directions, (2) had a known allergy, (3) had a disease for which the drug was contraindicated, and (4) took a drug that was not indicated, and possibly avoidable if there is a failure to monitor by a physician at reasonable time intervals and inadequate monitoring due to inability to see a physician (e.g., financial difficulties) (Nelson and Talbert, 1996)
Kongkaew C, et al. (2015)	(1) Drug-related morbidity (DRM) preceded by a recognisable drug therapy problem (DRP). (2) Given the DRP, the DRM would have been reasonably foreseeable. (3) The cause of DRM would have been identifiable with reasonable probability (Hallas criteria probable or definite for causality). (4) The cause of the DRM could have been reasonably controllable within the context and objectives of treatment. All four criteria must be fulfilled to confirm preventability
Gustafsson et al. (2016)	NA
Jolivot, et al. (2016)	NR

Abbreviations; NA=not applicable, NR=not reported

eTable 4. Meta-regression of included studies on hospital admission rate due to medication non-adherence

Covariate	Prevalence of hospital admission associated with medication non-adherence	
	Regression Equation β-Coefficient (95% CI)	***P*-value**
Age group (Reference: Elderly)	-1.08 (-3.73 to 1.57)	0.406
Geographical region (Reference: North America)	-1.21 (-2.42 to -0.01)	0.049
Method of detection (Reference: Interview)	0.97 (0.06 to 1.88)	0.038
Year of publication	-0.09 (-0.20 to 0.03)	0.106

eFigure 1. Funnel plot of included studies in the meta-analysis