ODPRN ONTARIO DRUG POLICY RESEARCH NETWORK

Comprehensive Research Plan:

Cognitive enhancers for the treatment of Alzheimer's disease

Systematic Review Unit

February 10, 2015

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ODPRN Drug Class Review Proposal: Systematic Review Unit

Comparative safety and effectiveness of cognitive enhancers for Alzheimer's Dementia: Protocol for a rapid update of a systematic review and network meta-analysis

Background

Alzheimer's dementia (AD) is a progressive neurodegenerative disorder characterized by cognitive decline associated with the presence of β-amyloid plaques in the AD patient's brain [1]. AD is the most common cause of dementia [2]. The prevalence of AD is increasing and it is expected to reach 42 million by 2040. The rate of increase is expected to be much higher in developing countries that will have as many as 60% of people living with dementia [3]. The global cost of dementia care in 2010 was estimated at US $604 billion and it is expected to rise to $1 trillion by 2030 [4].

Currently, there is no treatment for AD and disease management includes slowing progression, controlling symptoms, improving quality of life, and maintaining functional status [5]. Cognitive enhancer treatment for AD includes cholinesterase inhibitors (donepezil, rivastigmine, galantamine), and an N-methyl-D-aspartate receptor antagonist (memantine). Clinical trials have shown that donepezil and galantamine are effective in improving and maintaining cognitive and global function and activities of daily life, with minimum side effects that decrease with continued use and can be further minimized by taking with food. As for rivastigmine, studies have shown that it is effective in improving cognition and functional impairment without apparent side effects in AD patients [6]. Due to the scarcity of head-to-head trials comparing the safety and efficacy of these different cholinesterase inhibitors, there is no consensus regarding whether one particular treatment is superior toanother. The efficacy of cognitive enhancer medications has been examined in previous systematic reviews [7-9]. These reviews have only included randomized clinical trials (RCTs) which limit the ability to examine harms and generate 'real world' relevant findings. We are conducting this review to update a previous systematic review and network meta-analysis to determine the comparative effectiveness, and safety associated with cognitive enhancers versus, each other, no treatment, placebo, or best supportive care for AD and severe AD [5].

Objective

To examine the comparative safety and efficacy of cognitive enhancers (donepezil, rivastigmine, galantamine, and memantine) for patients with Alzheimer's dementia.

Study Questions:

1) What is the comparative safety and efficacy of cognitive enhancers (alone or in combination) versus placebo for patients with Alzheimer's dementia?

2) Which intervention (or combination) is the most effective and safe for patients with Alzheimer's dementia?

PICO Statement

The population, intervention, comparator, and outcome (PICO) statement, including the study designs of interest, is as follows.

Study Population:
Patients with Alzheimer's dementia (AD). We will report the way that AD was diagnosed across the included studies. Time permitting, we will consider conducting a sub-group analysis by severity of AD.

Intervention:
Interventions of interest are: cognitive enhancers namely donepezil, rivastigmine, galantamine, and memantine. We will focus our analysis on dosage approved for use in Canada. Time permitting, we will consider conducting a sub-group analysis on the dosage of these cognitive enhancers, if possible (e.g., low, medium, high).

Comparator Groups:
Eligible comparators are: donepezil, rivastigmine, galantamine, and memantine in any combination, no treatment, placebo, and best supportive care. Concomitant Alzheimer's disease medications will be included if all treatment arms receive the same interventions.

Outcome(s) of Interest:
Potential efficacy outcomes:

1. Cognition – Mini-Mental State Examination [MMSE], and Alzheimer's Disease Assessment Scale-cognition subscale [ADAS-cog]
2. Function – Alzheimer's Disease Cooperative Study activities of daily living inventory [ADCS-ADL]
3. Behaviour – Neuropsychiatric Inventory [NPI]
4. Global Status–Clinician's Interview-Based Impression of Change plus Caregiver Input [CIBIC-plus]
5. Mortality

Potential safety outcomes:

6. Serious Adverse Events
7. Bradycardia
8. Falls
9. Headaches
10. Vomiting
11. Diarrhea
12. Nausea

Notes: this list may be truncated if we identify many studies for inclusion, as this is a rapid review.

We might not perform a meta-analysis (or network meta-analysis) on all of these outcomes and will work with all stakeholders to select the most important efficacy and safety outcomes (4 in total) with sufficient data to conduct network meta-analysis. Prior to conducting network meta-analysis, we will ensure that all factors are considered (definition of outcomes, patient population, and disease severity) because this analysis only is valid when homogenous studies, and patient population are included.

Included study designs:
Included: RCTs and non-randomized studies

Other: We will limit inclusion to published studies written in English. Studies will be excluded if they are animal studies or if there is no quantitative data to abstract (e.g. letters, commentaries).

Methods

The figure in Appendix 1 displays the general approach that we use at the Li Ka Shing Knowledge Institute of St. Michael's Hospital to conduct a systematic review.

Protocol development

The Preferred Reporting Items for Systematic reviews and Meta-analysis for Protocols (PRISMA-P)

Statement will guide review reporting of our protocol [10]. A draft protocol will be circulated to receive feedback from key stakeholders including the OPDRN, clinicians, pharmacoepidemiologists, and systematic review methodologists.

Eligibility criteria

We use the Patients, Interventions, Comparators, Outcomes, Study designs and Time period (PICOST) framework (see above). The draft eligibility criteria can be found in Appendix 3.

Information sources and literature search

The previous systematic review by Tricco et al. [11] will be updated by conducting a comprehensive literature searche by an experienced librarian (Becky Skidmore) in consultation with the team. We will search the MEDLINE, EMBASE, and Cochrane Library electronic databases from September 2011 until January 2015. The preliminary MEDLINE search is presented in Appendix 3. The main (MEDLINE) search was peer reviewed by another experienced librarian using the Peer Review of Electronic Search Strategies (PRESS) checklist [12]. Literature saturation will be ensured by searching the reference lists of included studies and reference lists of relevant reviews [13].

Study selection process

To ensure reliability, a training exercise will be conducted prior to commencing screening. Using the inclusion and exclusion criteria, 25 titles and abstracts (also called citations) from the previous reviews will be screened by all team members. Inter-rater agreement for study inclusion will be calculated using percent agreement and if it is >90% across the team, we will proceed to the next stage. If poor agreement is found, the inclusion and exclusion criteria will be revised. Screening will only commence when the percent agreement is >90%. Two reviewers will screen citations for inclusion, independently (Level 1 screening). They will then independently review the full-text of potentially relevant articles to determine inclusion using the same inclusion and exclusion criteria (Level 2 screening). Conflicts will be resolved by discussion or the involvement of a third reviewer.

Data items and data abstraction process

We will abstract data on study characteristics (e.g., study design, year of conduct [if not reported, we will use the year of publication], sample size, setting [e.g., hospital, community, multi-center, single center], country of study conduct [if not reported, we will use the country of origin of the first author], duration of treatment, duration of follow-up, intervention and comparator dosage, monotherapy, combination therapy), participant characteristics (e.g., number of patients, age mean and standard deviation, AD severity, how AD was diagnosed, baseline cognition, co-morbidities). Finally, we will abstract the outcome results (e.g. cognition, function, behaviour, global status, mortality, harms, and withdrawal) for the longest duration of follow-up only, as this is the most conservative approach recommended by the Cochrane Collaboration [14]. The data will be extracted and stored in Excel. The draft data abstraction form can be found in Appendix 4. We will create a data abstraction information and elaboration sheet that will accompany reviewers while they are performing data abstraction. This will allow them to navigate the Excel file and result in greater inter-rater reliability. Furthermore, we will conduct a calibration exercise of the data abstraction form and cheat sheet amongst the team. This will entail the entire team conducting data abstraction on a random sample of 5 articles. Data abstraction will only commence when high agreement is achieved (e.g., only minor disagreements/recording errors noted across the team). The data abstraction form and cheat sheet will be revised, if low agreement is observed.

Since this rapid review is being completed in a short time-frame, only the outcome data will be

abstracted in duplicate. Discrepancies will be resolved by discussion or the involvement of a third reviewer. We suspect that multiple study publications may report data from the same study group (i.e., companion reports). When this occurs, the report with the most complete follow-up data will be included and used to abstract data.

Risk of bias appraisal process

We will appraise the included RCTs using the Cochrane Risk of Bias Tool [14]. This will be conducted by one reviewer since this rapid review is being completed on a short timeline.

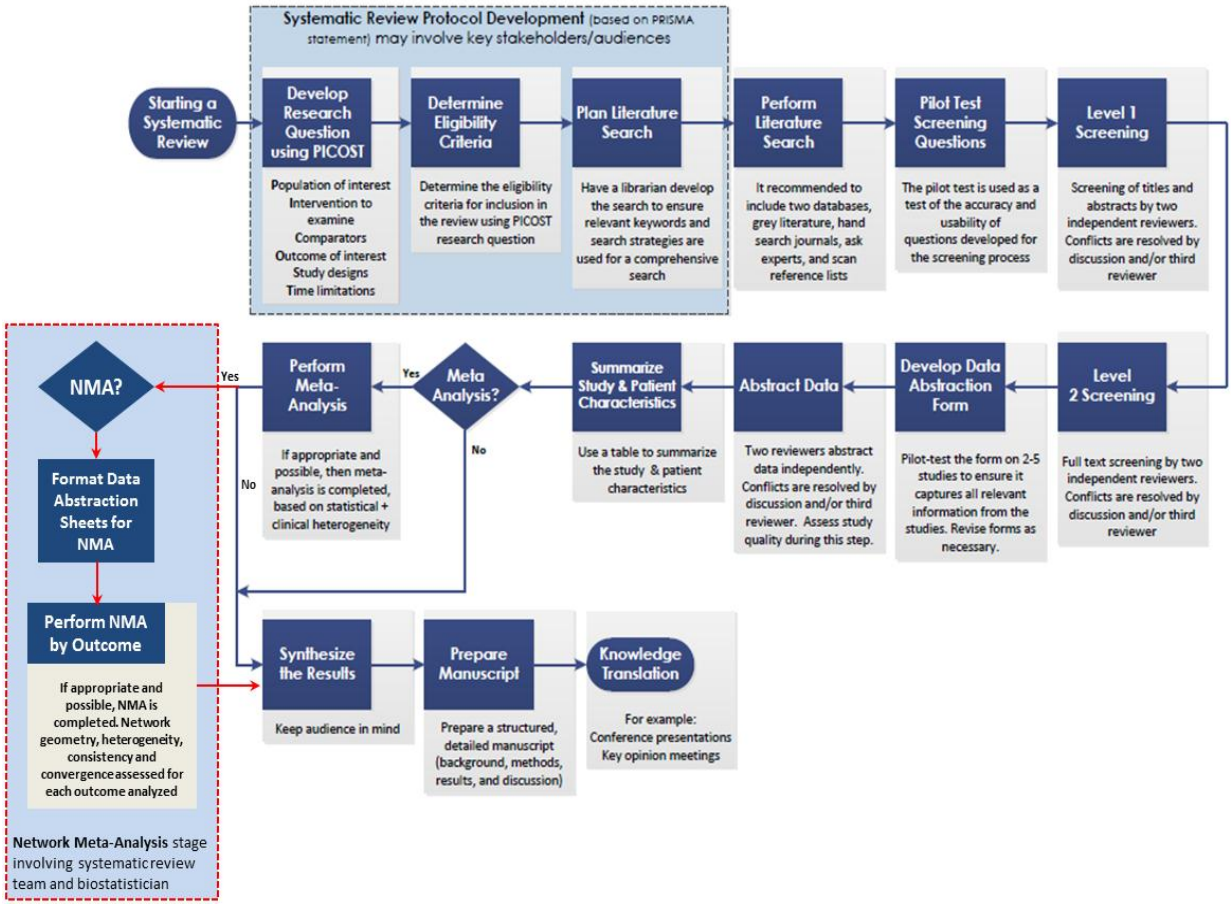
Synthesis of included studies

We will first describe our results, reporting study characteristics, patient characteristics, risk of bias results, and frequencies of outcomes across the included studies. Prior to considering meta-analysis, we will assess for statistical, clinical, and methodological heterogeneity. Meta-analysis will be analyzed in the R software [15]. The relative risk will be calculated for dichotomous values and the mean difference will be calculated for continuous variables [16].

Network meta-analysis will be conducted to derive the combined outcome effect size between each 2 comparisons, as well as rank the safety among all available interventions [17]. The placebo group will be used as a reference in the network meta-analysis. To facilitate the practicality of treatment comparisons, median rankings will be used as point estimates of intervention safety. We will use the NODE XL program to present the network meta-analysis results. Network meta-analysis will be conducted in WinBUGS, a Bayesian software program used to build complex statistical models using Markov Chain Monte Carlo simulation.

This will be conducted using a burn-in sample of 50000, followed by 100000 samples for inference. Convergence of the Markov chain Monte Carlo simulation will assessed with the Gelman-Rubin-Brooks plot and diagnostic test [18]. Default prior distributions (in all cases non-informative) will be adopted for all parameters in the model. Statistical significance will be expressed by 95% credible intervals that will be established using the 2.5 and 97.5 percentiles obtained via Markov Chain Monte Carlo simulation. We will interpret the 95% credible interval in a similar manner as confidence intervals are interpreted when they are derived using standard meta-analysis. The consistency of the results between direct versus indirect evidence will be compared using the node-splitting method [19].

APPENDIX 1: Systematic review process map



APPENDIX 2: Preliminary MEDLINE Search

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>, Embase<1980 to 2014 Week 50> Search Strategy:

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1 alzheimer$.mp.
2 "benign senescent forgetfulness".mp.
3 (cognit$ adj2 (impair$ or declin$ or deficit$ or degenerat$ or deteriorat$ or los$ or disorder$ or complain$ or disturb$)).mp.
4 (cerebr$ adj2 (impair$ or declin$ or deficit$ or degenerat$ or deteriorat$ or los$ or disorder$ or complain$ or disturb$)).mp.
5 (mental adj2 (impair$ or declin$ or deficit$ or degenerat$ or deteriorat$ or los$ or disorder$ or complain$ or disturb$)).mp.
6 (ne?rocognit$ adj2 (impair$ or declin$ or deficit$ or degenerat$ or deteriorat$ or los$ or disorder$ or complain$ or disturb$)).mp.)
7 (ne?ro-cognit$ adj2 (impair$ or declin$ or deficit$ or degenerat$ or deteriorat$ or los$ or disorder$ or complain$ or disturb$)).mp.
8 ((cognit$ or memory or cerebral or brain) adj2 (improv$ or enhanc$ or perform$ or process$ or function$ or rehabilitation or aid$ or stimulat$)).mp.
9 cognition.ti.
10 (confusion$ or confused).tw.
11 dement$.mp.
12 ("normal pressure hydrocephalus" and shunt$).mp.
13 "organic brain disease$".mp.
14 "organic brain syndrome".mp.
15 (presenil$ or pre-senil$ or senil$).tw.
16 Alzheimer Disease/
17 Cognition/de
18 Confusion/
19 Dementia/
20 or/1-19
21 abixa.tw.
22 aricept.tw.
23 (acetylcholinesteraseadj inhibitor$).tw.
24 axura.tw.
25 akatinol.tw.
26 (anticholinesterase? or anti-cholinesterase?).tw.
27 (cognitive adjenhanc$).mp.
28 (cholinesterase adj inhibitor$).mp.
29 ChEI.tw.
30 donepezil.mp.
31 ebixa.tw.
32 eranz.tw.
33 exelon.tw.
34 galant?amin$.tw.
35 lycoremine.tw.
36 memantin$.tw.
37 memox.tw.

38 namenda.tw.
39 nimvastid.tw.
40 nivalin$.tw.
41 "N-Methyl-D-aspartic acid receptor antagonist$".tw.
42 prometax.tw.
43 razadyne.tw.
44 reminyl.tw.
45 rivastigmine.mp.
46 exp Cholinesterase Inhibitors/
47 Galantamine/
48 Memantine/
49 Galantamin.rn.
50 Memantine.rn.
51 Donepezil.rn.
52 Donepezil Hydrochloride.rn.
53 Rivastigmine.rn.
54 or/21-53
55 20 and 54
56 exp Animals/ not (exp Animals/ and Humans/)
57 55 and 56
58 (comment or editorial or interview or news).pt.
59 (letter not (letter and randomized controlled trial)).pt.
60 57 not (58 or 59)
61 (201111* or 201112* or 2012* or 2013* or 2014*).ed.
62 60 and 61
63 alzheimer$.mp.
64 "benign senescent forgetfulness".mp.
65 (cognit$ adj2 (impair$ or declin$ or deficit$ or degenerat$ or deteriorat$ or los$ or disorder$ or complain$ or disturb$)).mp.
66 (cerebr$ adj2 (impair$ or declin$ or deficit$ or degenerat$ or deteriorat$ or los$ or disorder$ or complain$ or disturb$)).mp.
67 (mental adj2 (impair$ or declin$ or deficit$ or degenerat$ or deteriorat$ or los$ or disorder$ or complain$ or disturb$)).mp.
68 (ne?rocognit$ adj2 (impair$ or declin$ or deficit$ or degenerat$ or deteriorat$ or los$ or disorder$ or complain$ or disturb$)).mp.
69 (ne?ro-cognit$ adj2 (impair$ or declin$ or deficit$ or degenerat$ or deteriorat$ or los$ or disorder$ or complain$ or disturb$)).mp.
70 ((cognit$ or memory or cerebral or brain) adj2 (improv$ or enhanc$ or perform$ or process$ or function$ or rehabilitation or aid$ or stimulat$)).mp.
71 cognition.ti.
72 (confusion$ or confused).tw.
73 dement$.mp.
74 ("normal pressure hydrocephalus" and shunt$).mp.
75 "organic brain disease$".mp.
76 "organic brain syndrome".mp.
77 (presenil$ or pre-senil$ or senil$).tw
78 Alzheimer disease/
79 cognitive defect/
80 confusion/
81 dementia/

82 organic brain syndrome/
83 or/63-82
84 abixa.tw.
85 aricept.tw.
86 (acetylcholinesteraseadj inhibitor$).tw.
87 axura.tw.
88 akatinol.tw.
89 (anticholinesterase? or anti-cholinesterase?).tw.
90 (cognitive adjenhanc$).mp.
91 (cholinesterase adj inhibitor$).mp.
92 ChEI.tw.
93 donepezil.mp.
94 ebixa.tw.
95 eranz.tw.
96 exelon.tw.
97 galant?amin$.tw.
98 lycoremine.tw.
99 memantin$.tw.
100 memox.tw.
101 namenda.tw.
102 nimvastid.tw.
103 nivalin$.tw.
104 "N-Methyl-D-aspartic acid receptor antagonist$".tw.
105 prometax.tw.
106 razadyne.tw.
107 reminyl.tw.
108 rivastigmine.mp.
109 exp cholinesterase inhibitor/
110 donepezil/ or donepezil plus memantine/
111 galantamine/
112 memantine/
113 rivastigmine/
114 357-70-0.rn.
115 19982-08-2.rn.
116 120011-70-3.rn.
117 120014-06-4.rn.
118 rivastigmine.rn.
119 or/84-118
120 83 and 119
121 randomized controlled trial/ or controlled clinical trial/
122 exp "clinical trial (topic)"/
123 (randomi#ed or randomly or RCT$1 or placebo*).tw.
124 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw.
125 trial.ti.
126 or/121-125
127 120 and 126
128 exp controlled clinical trial/
129 exp "controlled clinical trial (topic)"/
130 (control* adj2 trial*).tw.
131 (nonrandom* or non-random* or quasi-random* or quasi-experiment*).tw.

132 (nRCT or nRCTs or non-RCT$1).tw.
133 (control* adj3 ("before and after" or "before after")).tw.
134 time series analysis/
135 (time series adj3 interrupt*).tw.
136 pretest posttest control group design/
137 (pre- adj3 post-).tw.
138 (pretest adj3 posttest).tw.
139 controlled study/
140 (control* adj2 stud$3).tw.
141 control group/
142 (control$ adj2 group$1).tw.
143 or/128-142
144 120 and 143
145 cohort analysis/
146 cohort.tw.
147 retrospective study/
148 longitudinal study/
149 prospective study/
150 (longitudinal or prospective or retrospective).tw.
151 follow up/
152 ((followup or follow-up) adj (study or studies)).tw.
153 observational study/
154 (observation$2 adj (study or studies)).tw.
155 population research/
156 ((population or population-based) adj (study or studies or analys#s)).tw.
157 ((multidimensional or multi-dimensional) adj (study or studies)).tw.
158 exp comparative study/
159 ((comparative or comparison) adj (study or studies)).tw.
160 exp case control study/
161 ((case-control* or case-based or case-comparison) adj (study or studies)).tw.
162 or/145-161
163 120 and 162
164 127 or 144 or 163
165 exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/
166 exp humans/ or exp human experimentation/ or exp human experiment/
167 165 not 166
168 164 not 167
169 editorial.pt.
170 letter.pt.not (letter.pt. and randomized controlled trial/)
171 168 not (169 or 170)
172 (2011112* or 2011113* or 201112* or 2012* or 2013* or 2014*).dd.
173 171 and 172
174 62 use prmz
175 173 use emez
176 174 or 175
177 remove duplicates from 176 [TOTAL UNIQUE HITS]
178 177 use prmz[MEDLINE UNIQUE HITS]
179 177 use emez[EMBASE UNIQUE HITS]

APPENDIX 3: Draft eligibility criteria

Level 1 screening:

1. Does this study include patients with Alzheimer's dementia?
   YES _____
   NO _____
   UNCLEAR _____

2. Is this an experimental study, quasi-experimental study, or observational epidemiology study?
   YES _____
   NO _____
   UNCLEAR _____

3. Does this study examine ANY of the following cognitive enhancers: donepezil, rivastigmine, galantamine, memantine [in any combination]?
   YES _____
   NO _____
   UNCLEAR _____

4. Does this study compare cognitive enhancers with placebo, no treatment, best supportive care or other cognitive enhancers [in any combination]?
   YES _____
   NO _____
   UNCLEAR _____

5. This study likely fulfills our eligibility criteria but is:
   Not written in English _____ (note: will not fully exclude from the review)
   A conference abstract (need to contact authors) _____
   A trial protocol (need to contact authors) _____
   A relevant systematic review (need to scan references) _____

Level 2 screening:

1. Does this study include patients with Alzheimer's dementia?
   YES _____
   NO _____
   UNCLEAR _____

2. Is this an experimental study, quasi-experimental study, or observational epidemiology study?
   YES _____
   NO _____
   UNCLEAR _____

3. Does this study examine ANY of the following cognitive enhancers: donepezil, rivastigmine, galantamine, memantine [in any combination]?
   YES _____
   NO _____
   UNCLEAR _____

4. Does this study compare cognitive enhancers with placebo, no treatment, best supportive care or other cognitive enhancers [in any combination]?
   YES _____
   NO _____
   UNCLEAR _____

5. Does this study report on ANY of the following outcomes that were prioritized by the ODPRN: e.g., cognition, function, behaviour, global status, mortality, harms, and withdrawal?
   YES _____
   NO _____
   UNCLEAR _____

6. This study likely fulfills our eligibility criteria but:
   Is not written in English _____ (note: will not fully exclude from the review)
   Is a conference abstract (need to contact authors) _____
   Is a trial protocol (need to contact authors) _____
   Is a relevant systematic review (need to scan references) _____
   Does not contain abstractable data (need to contact authors) _____

➡ If you answer NO to any of these questions, the citation/study will be excluded. All other citations/studies will be included. We will keep track of reviews that have potentially relevant material and will scan their reference lists to ensure all studies have been captured.

APPENDIX 4: Draft data abstraction form

Study Characteristics

1. First author and year of publication
2. Reference ID number
3. Year of study conduct
4. Country of study conduct (if not reported, use the country of origin of the first author)
5. Study design
6. Study conduct period
7. Trial duration
8. Setting (e.g., hospital, community, multi-center, single center)
9. Sample size
10. Duration of treatment
11. Total duration of follow-up (includes duration of treatment and subsequent follow-up)

Patient Characteristics

12. Eligibility criteria
13. Qualifying score(s)
14. AD Severity
15. Mean age and standard deviation (if not reported, the range or interquartile range will be used)
16. Percent Female

Outcome results

17. Cognition(e.g., intervention, dose, sample size, mean, variance)
18. Function (e.g.,intervention, dose, sample size, mean, variance)
19. Behaviour(e.g.,intervention, dose, sample size, mean, variance)
20. Global status (e.g.,intervention, dose, sample size, mean, variance, category reported, # in each category)
21. Mortality (e.g., intervention, dose, sample size, # of patients)
22. Nausea (e.g.,intervention, dose, sample size, # of patients)
23. Diarrhea (e.g., intervention, dose, sample size, # of patients)
24. Vomiting (e.g., intervention, dose, sample size, # of patients)
25. Serious adverse events (e.g., intervention, dose, sample size, # of patients)
26. Headaches (e.g., intervention, dose, sample size, # of patients)
27. Falls (e.g., intervention, dose, sample size, # of patients)
28. Bradycardia(e.g., intervention, dose, sample size, # of patients)

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