Effective Health Care

Treatment of Adults with Clinical Alzheimer's-type Dementia (CATD)

Results of Topic Selection Process & Next Steps

The nominator, AAFP is interested in using a new systematic review on Clinical Alzheimer's-type Dementia to inform a clinical practice guideline.

This topic will go forward as a new systematic review. The scope of this topic, including populations, interventions, comparators, and outcomes, will be further developed in the refinement phase. When key questions have been drafted, they will be posted on the AHRQ Web site and open for public comment. To sign up for notification when this and other Effective Health Care (EHC) Program topics are posted for public comment, please go to https://effectivehealthcare.ahrq.gov/email-updates

Topic Brief

Topic: Treatment of Adults with Clinical Alzheimer's-type Dementia (CATD)

Nomination Date: 08/23/2017

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Conflict of Interest:
The investigator does not have any affiliations or financial involvement that conflicts with the material presented in this report.

Findings:

- This nomination fulfilled all selection criteria
- While we found a number of reviews, they only cover pieces of the revised nomination scope.
- This topic is of interest to many groups including provider groups and Federal agencies.
- The review should include diagnosis of mild cognitive impairment and CATD because it was excluded from the scope of the in-process systematic review for the USPSTF.

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Background

Dementia is severely disabling, impacting quality of life and abilities, potentially to the point of institutionalization. The burden is not only on the patient, but also on the family and other caregivers. Moreover, the financial burden is high. RAND estimated that, in 2010, the per-patient cost was $41,689-$56,290 per year; the total US cost was estimated at $109 billion for care, and $159-$215 billion if the value included informal care[1]. The prevalence of dementia ranges from 5 to 7%[2]. There are a variety of pharmacologic and nonpharmacologic treatments for individuals with Clinical Alzheimer's Type Dementia (CATD) aimed at maintaining cognition and quality of life and controlling behavioral disturbances; however, there is no agreement as to the accuracy of the diagnostic tests and which intervention(s) are most effective and have the fewest harms, when to initiate treatment, and when to end treatment.

The nominator is interested in using a systematic review process to inform an update of their 2008 practice guideline on the treatment of adults with Clinical Alzheimer's-type Dementia (CATD).

Nominator and Stakeholder Engagement: The original nomination included questions on diagnosis and Mild Cognitive Impairment (MCI). However these areas may be covered by an in-process systematic review to inform a US Preventive Services Task Force recommendation on screening, diagnosis and treatment [3]; and AHRQ systematic review on interventions for MCI [4].After consultation with the nominator these areas were excluded from the scope of this assessment.

The key questions are:

KQ 1a: What is the comparative effectiveness and harms of pharmacologic and nonpharmacologic interventions in adults with clinical Alzheimer's-type dementia (CATD), for:

i. Improving cognition or slowing cognitive decline?
ii. Improving QoL and ADL or slowing decline?

KQ 1b: Do the harms or effectiveness differ as a function of patient characteristics (i.e., age, sex, race/ethnicity, family history, education, socioeconomic status, risk factor status)?

KQ 2: What is the comparative effectiveness and harms of pharmacologic and nonpharmacologic interventions aimed at preventing and responding to agitation/aggression and other behavioral disturbances among adults with clinical Alzheimer's-type dementia (CATD):

i. Among community-dwelling adults
ii. In nursing home and assisted living settings?

Table 1. Key Questions and PICOTs

PICOTS	KQ1 (cognitive decline, community and assisted living)	KQ2 (agitation and aggression)
Population	Adults with CATD	Adults with CATD
Intervention	• FDA- approved pharmacologic interventions aimed at improving cognition or slowing decline, improving QoL and ADL or slowing decline (donepezil, galantamine, memantine, rivastigmine, Aricept, Razadyne, Namenda, Exelon, Namzaric) • Nonpharmacologic interventions aimed at improving cognition or slowing decline, improving QoL and ADL or slowing decline (including respite care and day care interventions)	• Pharmacologic interventions to prevent and respond to behavioral disturbances (e.g. . antipsychotics, sedative hypnotics) • Nonpharmacologic interventions to prevent and respond to behavioral disturbances (such as herbal supplements such as ginko biloba, music, light, pet, reminiscence, or psychodynamic interpersonal therapy; nighttime home monitoring systems; Snoezelen® multisensory environments)
Comparators	• Usual care (as specified by trial investigators) • Attention control or placebo • Other nonpharmacologic interventions • Other pharmacologic interventions	• Usual care (as specified by trial investigators) or no treatment • Attention control or placebo • Other nonpharmacologic interventions • Other pharmacologic interventions
Outcomes	**Final health or patient-centered outcomes:** • Cognitive improvement, cognitive stability, cognitive decline as determined by validated cognitive test results • QoL, as determined by SF-36 **Adverse effects of intervention(s):** • Adverse effects of interventions (such as increased symptoms including depression, anxiety and wandering) • Cost	**Final health or patient-centered outcomes:** • Frequency, duration, and severity of aggressive behaviors; • General behavior of people with dementia; • Distress; • Quality of life; • Injuries to residents, staff, others **Secondary Outcomes** • Staff distress, burden, quality of life **Intermediate Outcomes** • Staff behavior change • Reduction in antipsychotic use **Adverse Effects of Intervention(s)** • Adverse effects of interventions (such as increased symptoms including depression, anxiety and wandering) • Cost
Settings	• Community-dwelling adults (people with dementia living at home) • Adults in assisted living	• Nursing homes and assisted living facilities • Community-dwelling adults

Abbreviations: CATD = Alzheimer's-type dementia; KQ=key questions; MCI: Mild Cognitive Impairment

Methods

We assessed the nomination for priority for a systematic review or other AHRQ EHC report with a hierarchical process using established selection criteria (Appendix A). Assessment of each criteria determined the need for evaluation of the next one.

1. Determine the *appropriateness* of the nominated topic for inclusion in the EHC program.
2. Establish the overall *importance* of a potential topic as representing a health or healthcare issue in the United States.
3. Determine the *desirability of new evidence review* by examining whether a new systematic review or other AHRQ product would be duplicative.
4. Assess the *potential impact* a new systematic review or other AHRQ product.
5. Assess whether the *current state of the evidence* allows for a systematic review or other AHRQ product (feasibility).
6. Determine the *potential value* of a new systematic review or other AHRQ product.

Appropriateness and Importance

We assessed the nomination for appropriateness and importance.

Desirability of New Review/Duplication

We updated the search for high-quality, completed or in-process evidence reviews published since the previous assessment (June 1, 2016 to October 18, 2017). See Appendix B for sources searched.

Impact of a New Evidence Review

The impact of a new evidence review was qualitatively assessed by analyzing the current standard of care, the existence of potential knowledge gaps, and practice variation. We considered whether it was possible for this review to influence the current state of practice through various dissemination pathways (practice recommendation, clinical guidelines, etc.).

Feasibility of New Evidence Review

For the feasibility search, we conducted a literature search in PubMed and PsycInfo for the past 5 years ending October 2017. While we found a systematic review (Nonpharmacologic Interventions for Agitation and Aggression in Dementia, https://ahrq-ehc-application.s3.amazonaws.com/media/pdf/dementia-agitation-aggression_research.pdf) [6] relevant to KQ 2, we used the same timeframe for the entire feasibility search ensure that we captured studies comparing pharmacologic to non-pharmacologic interventions. See Appendix C for search strings.

Value

We assessed the nomination for value. We considered whether or not the clinical, consumer, or policymaking context had the potential to respond with evidence-based change; and if a partner organization would use this evidence review to influence practice.

Compilation of Findings

We constructed a table with the selection criteria and our assessments (Appendix A).

Results

Appropriateness and Importance

This is an appropriate and important topic. By 2020, the CDC estimates that older adults will account for approximately 20% of the US population.1 The prevalence of dementia ranges from 5 to 7%.

Desirability of New Review/Duplication

A new evidence review would not be duplicative of an existing product. We identified three AHRQ systematic reviews and other reviews related to the original nomination. However, these reviews are not duplicative, because they only review a pieces of the scope. There are no completed or in-process systematic reviews examining the topics covered in the current key questions. See Table 2, Duplication column.

Impact of a New Evidence Review

A new systematic review may have high impact. There is a large breadth of interventions available and uncertainty about their comparative effectiveness and harms for treating and managing individuals with CATD.

Feasibility of a New Evidence Review

A new evidence review is feasible. We projected a large evidence base. See Table 2, Feasibility column.

Table 2. Key Questions and Results of Duplication and Feasibility Search

Key Question	Duplication (Completed or In-Process Evidence Reviews) (October 2014-October 2017)	Feasibility (Published and Ongoing Original Research) (October 2012-October 2017)
KQ 1 comparative effectiveness and harm of pharmacologic and nonpharmacologic interventions for cognitive decline	Total number of completed systematic reviews – 11 • AHRQ: o Pharm and NonPharm: 1 [4] • Medline and PsycINFO and Cochrane: o Pharm: 4 [4, 7-9] o NonPharm: 6 [4, 10-14]	Size/scope of review Relevant Studies Identified: • Pharm: 6 [15-20] • NonPharm: 17 [21-37] ClinicalTrials.gov Relevant Trials: 6 • Pharm: o Recruiting: 1 [38] o Completed: 1 [39] • NonPharm: o Completed:3 [40-42] o Not Yet Recruiting: 1 [43]
KQ 2: comparative effectiveness and harms of nonpharmacologic interventions and pharmacologic interventions to prevent and respond to agitation/aggression	Total number of completed systematic reviews: 12 • AHRQ: o NonPharm: 1 [6] • Medline and PsycINFO and Cochrane: o Pharm: 6 [44-50] o NonPharm: 5 [47, 51-54]	Size/scope of review Relevant Studies Identified: • Pharm: [15, 55-66] • NonPharm: [24, 25, 29, 67-76] ClinicalTrials.gov Relevant Trials: 2 • Pharm: 0 • NonPharm: o Completed: 2 [40, 42] (Note these overlap with KQ1)

Abbreviations: Pharm= Pharmacologic Intervention; NonPharm= Nonpharmacologic Intervention; KQ=Key Question

Value

The potential for value is high. Provider groups are interested in using the findings of a systematic review to inform clinical care.

Summary of Findings

- This nomination meets all selection criteria.
- Previous reviews covered portions of the nomination but not the entire scope
- There are two guideline groups who are interested in using the review to inform a practice guideline. In addition, other Federal agencies would be interested in the report findings.
- While diagnosis of mild cognitive impairment and CATD was initially excluded because of the in-process review for the USPSTF, their final research plan was published after this assessment and does not include diagnosis. This should be included in the scope of this review.

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https://dx.doi.org/10.3310/hta16480

Appendix A. Selection Criteria Summary

Selection Criteria	Supporting Data
1. Appropriateness	
1a. Does the nomination represent a health care drug, intervention, device, technology, or health care system/setting available (or soon to be available) in the U.S.?	Yes, this topic represents a health care drug and intervention available in the U.S.
1b. Is the nomination a request for a systematic review?	Yes, this topic is a request for a systematic review.
1c. Is the focus on effectiveness or comparative effectiveness?	The focus of this review is on both effectiveness and comparative effectiveness.
1d. Is the nomination focus supported by a logic model or biologic plausibility? Is it consistent or coherent with what is known about the topic?	Yes, it is biologically plausible. Yes, it is consistent with what is known about the topic.
2. Importance	
2a. Represents a significant disease burden; large proportion of the population	By 2020, the CDC estimates that older adults will account for approximately 20% of the US population.1 The prevalence of dementia ranges from 5 to 7%.
2b. Is of high public interest; affects health care decision making, outcomes, or costs for a large proportion of the US population or for a vulnerable population	Yes, this topic affects heath care decisions for a large, vulnerable population.
2c. Represents important uncertainty for decision makers	Yes, this topic represents important uncertainty for decision makers.
2d. Incorporates issues around both clinical benefits and potential clinical harms	Yes, this nomination addresses both benefits and potential harms of pharmacological and nonpharmacological treatments for CATD and behavioral disturbances associated with CATD.
2e. Represents high costs due to common use, high unit costs, or high associated costs to consumers, to patients, to health care systems, or to payers	Yes this mental health diagnosis represents high cost due to the high rate of health and interpersonal dysfunction.
3. Desirability of a New Evidence Review/Duplication	
3. Would not be redundant (i.e., the proposed topic is not already covered by available or soon-to-be available high-quality systematic review by AHRQ or others)	We identified three AHRQ systematic reviews related to the original nomination. As a result we excluded diagnosis and MCI population, We also found other systematic reviews that addressed pieces of the scope; however, these reviews are not duplicative, because they only review a pieces of the scope. There are no completed or in-process systematic reviews examining the topics covered in the current key questions.
4. Impact of a New Evidence Review	
4a. Is the standard of care unclear (guidelines not available or guidelines inconsistent, indicating an information gap that may be addressed by a new evidence review)?	Yes, the standard of care is unclear because of the breadth of interventions available and uncertainty about their comparative effectiveness and harms.

Selection Criteria	Supporting Data
4b. Is there practice variation (guideline inconsistent with current practice, indicating a potential implementation gap and not best addressed by a new evidence review)?	Yes, there is practice variation because the standard of care is unclear, and guidelines need to be updated.
5. Primary Research	
5. Effectively utilizes existing research and knowledge by considering: - Adequacy (type and volume) of research for conducting a systematic review - Newly available evidence (particularly for updates or new technologies)	Size/scope of review: Our search of PubMed and PsycInfo resulted in a total of ~350 unique titles. Upon title and abstract review, we identified a total of 49 studies potentially relevant to the key questions in the nomination. Given that the search was not comprehensive, we estimate the size of a new review as would be a medium. ClinicalTrials: We identified 6 open or recently closed relevant clinical trials on ClinicalTrials.gov.
6. Value	
6a. The proposed topic exists within a clinical, consumer, or policy-making context that is amenable to evidence-based change	Yes, this topic will inform clinical decision-making on screening, treating CATD.
6b. Identified partner who will use the systematic review to influence practice (such as a guideline or recommendation)	Yes, AAFP and ACP will use a systematic review to update their practice parameters on the treatment of CATD.

Appendix B. Duplication

Sources: Search for Duplication
AHRQ: Evidence reports https://www.effectivehealthcare.ahrq.gov/products-tools
Cochrane Systematic Reviews and Protocols http://www.cochranelibrary.com/
PsycINFO http://www.ovid.com/site/catalog/databases/139.jsp
Medline/Pubmed https://www.nlm.nih.gov/bsd/pmresources.html
HTA (CRD database): Health Technology Assessments http://www.crd.york.ac.uk/crdweb/
PROSPERO Database (international prospective register of systematic reviews and protocols) http://www.crd.york.ac.uk/prospero/

Appendix C. Search Strategy Results (Feasibility)

Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Date Searched: October 17, 2017

Searched by: Robin Paynter, MLIS

#	Medline KQ1	Results
1	Alzheimer Disease/	85368
2	alzheimer*.ti,kf.	71126
3	or/1-2	100668
4	Drug Therapy/ or Activities of Daily Living/ or Quality of life/ or ((metacognit* or meta-cognit* or cognit* or mental* or brain or memory or social or psychosocial* or perceptual or "quality of life" or QoL or (activit* adj3 (life or living)) or ADL) adj5 (activit* or train* or stimulat* or intervention* or engag* or rehab* or protect* or delay* or reduc* or decreas* or effect* or lower* or decline or modif* or change or changing or stop* or improv* or increas* or enhanc* or rais* or program* or therap* or pharmacotherap* or pharmaco-therap* or pharmacolog*)).ti.	355188
5	Independent living/ or exp Home care services/ or Home nursing/ or Respite care/ or Adult Day Care Centers/ or Assisted Living Facilities/ or (community-dwelling or homecare or home-care or independent-living or nonresident* or non-resident* or respite-care or "adult day care center*" or "assisted living").ti,kf.	57632
6	and/3-5	284
7	limit 6 to english language	248
8	(2012* or 2013* or 2014* or 2015* or 2016* or 2017*).dc.	7014317
9	and/7-8	65
10	remove duplicates from 9	60
11	((adverse or unintended or unintentional or unwanted or unexpected or undesirable) adj2 (interaction$ or response$ or effect$ or event$ or reaction$ or outcome$)).ti,ab.	389187

#	Medline KQ1	Results
12	(adrs or ades).ti,ab.	4412
13	drug safety.ti,ab.	3763
14	(drug surveillance or ((postmarketing or post marketing) adj2 surveillance)).ti,ab.	2989
15	tolerability.ti,ab.	45568
16	(harm or harms or harmful).ti,ab.	93217
17	product surveillance, postmarketing/	6824
18	adverse drug reaction reporting systems/	7019
19	exp Drug Hypersensitivity/	44804
20	iatrogenic disease/	16014
21	exp drug toxicity/	109218
22	Abnormalities, Drug-Induced/	15082
23	treatment emergent.ti,ab.	3671
24	drug toxicity.ti,ab.	4802
25	(iatrogenic or iatrogenesis).ti,ab.	28361
26	complication*.ti.	127006
27	toxicity.ti.	78691
28	safety.ti.	104370
29	safe.ti.	24170

#	Medline KQ1	Results
30	or/11-29	933293
31	10 and 30	5
32	10 not 31	55
33	3 and 4 and 5 and 8	75
34	limit 33 to (meta analysis or systematic reviews)	3

#	Medline KQ2	Results
1	Alzheimer Disease/	85368
2	alzheimer*.tw,kf.	128121
3	or/1-2	139938
4	behavioral symptoms/ or aggression/ or agonistic behavior/ or bullying/ or problem behavior/ or psychomotor agitation/ or violence/ or physical abuse/ or anxiety/	138313
5	(aggress* or agitat* or bullying or combative or violent or violence or "challenging behav*" or anxiety or distress or restlessness).tw,kf.	496101
6	or/4-5	540272
7	and/3,6	4336
8	residential facilities/ or assisted living facilities/ or homes for the aged/ or exp nursing homes/ or long-term care/	67316
9	(resident or residents or (resident* adj3 (facilit* or care)) or "nursing home*" or assisted-living or "long-term care").tw,kf.	170279

#	Medline KQ2	Results
10	or/8-9	205239
11	independent living/ or exp home care services/	48487
12	(community-dwelling or homecare or home-care or independent-living or nonresident* or non-resident*).tw,kf.	40235
13	or/11-12	76491
14	randomized controlled trial.pt.	497191
15	controlled clinical trial.pt.	99259
16	randomized controlled trials as topic/	121887
17	random allocation/	99667
18	double-blind method/	157579
19	single-blind method/	26580
20	clinical trial.pt.	548083
21	exp clinical trial as topic/	332292
22	(clin* adj25 trial*).ti,ab.	406684
23	((single* or doubl* or trebl* or tripl*) adj25 (blind* or mask*)).ti,ab.	174668
24	placebos/	36435
25	placebo*.ti,ab.	209307
26	random*.ti,ab.	1016593
27	research design/	101160

#	Medline KQ2	Results
28	comparative study/	1908814
29	exp evaluation studies/	242756
30	follow up studies/	627556
31	prospective studies/	497496
32	(control* or prospective* or volunteer*).ti,ab.	4088971
33	or/14-32	7079206
34	7 and 33	1917
35	limit 34 to english language	1802
36	(2012* or 2013* or 2014* or 2015* or 2016* or 2017*).dc.	7014317
37	and/35-36	633
38	remove duplicates from 37	564
39	10 and 37	56
40	13 and 37	29
41	((adverse or unintended or unintentional or unwanted or unexpected or undesirable) adj2 (interaction$ or response$ or effect$ or event$ or reaction$ or outcome$)).ti,ab.	389187
42	(adrs or ades).ti,ab.	4412
43	drug safety.ti,ab.	3763
44	(drug surveillance or ((postmarketing or post marketing) adj2 surveillance)).ti,ab.	2989
45	tolerability.ti,ab.	45568

#	Medline KQ2	Results
46	(harm or harms or harmful).ti,ab.	93217
47	product surveillance, postmarketing/	6824
48	adverse drug reaction reporting systems/	7019
49	exp Drug Hypersensitivity/	44804
50	iatrogenic disease/	16014
51	exp drug toxicity/	109218
52	Abnormalities, Drug-Induced/	15082
53	treatment emergent.ti,ab.	3671
54	drug toxicity.ti,ab.	4802
55	(iatrogenic or iatrogenesis).ti,ab.	28361
56	complication$.ti.	127006
57	toxicity.ti.	78691
58	safety.ti.	104370
59	safe.ti.	24170
60	or/41-58	911862
61	7 and 60	422
62	limit 61 to english language	400
63	(201507* or 201508* or 201509* or 201510* or 201511* or 201512* or 2016* or 2017*).dc.	3203699

#	Medline KQ2	Results
64	and/62-63	64
65	remove duplicates from 64	54
66	10 and 65	4
67	13 and 65	1
68	7 and 36	1701
69	limit 68 to (meta analysis or systematic reviews)	106
70	limit 69 to english language	101
71	remove duplicates from 70	82

Ovid PsycINFO 1806 to October Week 2 2017

Date Searched: October 17, 2017

Searched by: Robin Paynter, MLIS

#	**PsycINFO KQ1**	**Results**
1	alzheimer's disease/	40901
2	alzheimer*.ti.	27803
3	or/1-2	41476
4	exp Drug Therapy/ or ((metacognit* or meta-cognit* or cognit* or mental* or brain or memory or social or psychosocial* or perceptual or "quality of life" or QoL or (activit* adj3 (life or living)) or ADL) adj5 (activit* or train* or stimulat* or intervention* or engag* or rehab* or protect* or delay* or reduc* or decreas* or effect* or lower* or decline or modif* or change or changing or stop* or improv* or increas* or enhanc* or rais* or program* or therap* or pharmacotherap* or pharmaco-therap* or pharmacolog*)).ti.	217070
5	caregivers/ or caregiver burden/ or elder care/ or home care/ or home care personnel/ or respite care/ or retirement communities/ or (community-dwelling or homecare or home-care or independent-living or nonresident* or non-resident* or respite-care or "adult day care center*" or "assisted living").ti,ab.	48022
6	and/3-5	286
7	("2012" or "2013" or "2014" or "2015" or "2016" or "2017").yr.	1082441
8	and/6-7	98
9	limit 8 to english language	98
10	remove duplicates from 9	98
11	limit 10 to journal article	85
12	limit 10 to ("0830 systematic review" or 1200 meta analysis)	2

#	PsycINFO KQ2	Results
1	alzheimer's disease/	40901
2	alzheimer*.ti,ab.	51627
3	or/1-2	53101
4	aggressiveness/ or aggressive behavior/ or attack behavior/ or exp bullying/ or violence/ or behavior problems/ or patient violence/ or workplace violence/ or agitation/ or exp anxiety/ or distress/ or restlessness/	165037
5	(aggress* or agitat* or bullying or combative or violent or violence or "challenging behav*" or anxiety or distress or restlessness).ti,ab.	350894
6	or/4-5	384493
7	and/3,6	2833
8	nursing homes/ or residential care institutions/ or long term care/	20723
9	("residential facilit*" or "residential care" or resident or residents or "nursing home*" or "assisted living" or "long-term care").ti,ab.	52525
10	or/8-9	59961
11	caregivers/ or caregiver burden/ or elder care/ or home care/ or home care personnel/ or respite care/ or retirement communities/	34130
12	(community-dwelling or independent living or homecare or non-resident).ti,ab.	10596
13	or/11-12	43895

#	PsycINFO KQ2	Results
14	limit 7 to "0300 clinical trial"	77
15	(clin* adj25 trial*).ti,ab.	36456
16	((single* or doubl* or trebl* or tripl*) adj25 (blind* or mask*)).ti,ab.	24646
17	placebo*.ti,ab.	36653
18	random*.ti,ab.	170703
19	(control* or prospective* or volunteer*).ti,ab.	673522
20	or/14-19	791589
21	and/7,20	926
22	limit 21 to english language	881
23	("2012" or "2013" or "2014" or "2015" or "2016" or "2017").yr.	1082441
24	and/22-23	282
25	remove duplicates from 24	282
26	and/10,24	23
27	and/13,24	48
28	((adverse or unintended or unintentional or unwanted or unexpected or undesirable) adj2 (interaction* or response* or effect* or event* or reaction* or outcome*)).ti,ab.	37491
29	(adrs or ades).ti,ab.	342
30	drug safety.ti,ab.	220
31	(drug surveillance or ((postmarketing or post marketing) adj2 surveillance)).ti,ab.	240

#	PsycINFO KQ2	Results
32	tolerability.ti,ab.	6361
33	(harm or harms or harmful).ti,ab.	37176
34	treatment emergent.ti,ab.	1089
35	drug toxicity.ti,ab.	163
36	(iatrogenic or iatrogenesis).ti,ab.	1766
37	complication*.ti.	2124
38	toxicity.ti.	1473
39	safety.ti.	10905
40	safe.ti.	2186
41	or/28-40	93277
42	and/7,41	211
43	limit 42 to english language	205
44	("2015" or "2016" or "2017").yr.	510881
45	and/43-44	24
46	remove duplicates from 45	24
47	and/10,45	3
48	and/13,45	3
49	or/10,13	98903

#	PsycINFO KQ2	Results
50	3 and 6 and 49	836
51	limit 50 to ("0830systematic review" or 1200 meta analysis)	7