Skal eldre med mild depresjon tilbys antidepressiver?

Problem: Eldre med mild depresjon
Tiltak: Antidepressiver
Sammenlikning: Ikke antidepressiver
Setting: Primærhelsetjenesten
Perspektiv: Individnivå (lege - pasient)

Bakgunn: Forekomsten av depresjon stiger med alderen og med summen av tilleggslidelser og ca 15 % av eldre har depresjon, De fleste med depressiv episode har milde former, 2-4 % antas å ha alvorlig depresjon. Tall sammenholdt fra reseptregisteret og SSB indikerer at 13 % av personer mellom 65 og 79 år bruker antidepressiver, og 14 % fra 80 og over. Selv om vi ikke kjenner indikasjonen, må vi anta at de fleste får antidepressiver på grunn av depresjon. Derfor må vi også anta at mange eldre med milde depresjoner bruker antidepressiver.

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?**	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ | ***Varies*** ☐		Det er vurderinger både av nytte, skade, pasientsikkerhet og helseøkonomi som ligger til grunn for prioriteringen. Jo mindre alvorlig tilstanden er, og jo mindre effekten av tiltaket er, jo større vekt må vi legge på mulige bivirkninger. Medikamentell behandling av tilstander med usikker effekt innebærer også samfunnsøkonomiske utgifter som med fordel kan brukes til andre mer effektive tiltak.

BENEFITS & HARMS OF THE OPTIONS

CRITERIA	JUDGEMENTS
What is the overall certainty of this evidence?	No included studies ☐ | Very low ☐ | Low ☐ | Moderate ☒ | High ☐
Is there important uncertainty about how much people value the main outcomes?	Important uncertainty or variability ☐ | Possibly important uncertainty or variability ☐ | Probably no important uncertainty or variability ☒ | No important uncertainty or variability ☐ | No known undesirable outcomes ☐
Are the desirable anticipated effects large?	No ☒ | Probably No ☐ | Uncertain ☐ | Probably Yes ☐ | Yes ☐ | Varies ☐
Are the undesirable anticipated effects small?	No ☒ | Probably No ☐ | Uncertain ☐ | Probably Yes ☐ | Yes ☐ | Varies ☐
Are the desirable effects large relative to undesirable effects?	No ☐ | Probably No ☒ | Uncertain ☐ | Probably Yes ☐ | Yes ☐ | Varies ☐

RESEARCH EVIDENCE

Summary of findings:

Antidepressants for elderly with mild depression

Bibliography: Adult population: [1] Geriatric population:[2] Hazard/unintended effects: [3]

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects: Risk with Control	Anticipated absolute effects: Risk difference with Antidepressants (95% CI)
Symptom change in patients with mild to moderate depression (baseline Hamilton Depression Rating Scale 18 or less)	0 (6 studies[2]) 6-11 weeks	⊕⊕⊕⊖ **MODERATE** [11] due to imprecision		The mean symptom change in patients with mild to moderate depression (baseline Hamilton Depression Rating Scale (HDRS) score 18 or less) in the intervention groups was **0.11 standard deviations lower** (0.41 lower to 0.18 higher)[1]	
Response rate - geriatric studies HDRS	2000 (4 studies[10]) 6 weeks	⊕⊕⊖⊖ **LOW**[4,6,11] due to imprecision, publication bias	**OR 1.42** (0.92 to 2.18)	**274 per 1000**[3]	**75 more per 1000** (from 16 fewer to 177 more)
Remission rates - geriatric studies HDRS	2000 (4 studies[10]) 6 weeks	⊕⊕⊖⊖ **LOW**[4,6,11] due to imprecision,publication bias	**OR 1.26** (0.78 to 2.03)	**200 per 1000**[3]	**40 more per 1000** (from 37 fewer to 137 more)
Depressive symptoms - geriatric studies mild depression	960 (4 studies[10]) 6 weeks	⊕⊕⊕⊖ **MODERATE** [11] due to imprecision		The mean HDRS score was **- 5.42**	The mean HDRS score was **1.47 lower** (3.20 lower to 0.26 higher)[12]
All cause mortality (SSRI vs no ADs) Rates per patient-	241757 (1 study) 1-12 years	⊕⊕⊖⊖ **LOW**[15]	**HR 1.54** (1.48 to 1.59)[13]	**48 per 1000 patient-years**[14]	**25 more per 1000 patient-years** (from 22 more to 27 more)

ADDITIONAL CONSIDERATIONS

Vi har liten sikker kunnskap om hvordan eldre pasienter med depresjon vektlegger mulig bedring av symptomer ved depresjon, versus mulige bivirkninger ved bruk av antidepressiver.
Ved milde depresjoner er sannsynligheten for klinisk ønsket effekt (nytte) liten, og vi må derfor vekte potensielle bivirkninger (skade) mer. Coupland C et al (2011) demonstrerer i en stor retrospektiv studie basert på data fra elektroniske pasientjournaler fra 570 legepraksiser i UK at nyere antidepressiver har like stor forekomst av alvorlige bivirkninger som eldre antidepressiver, og risikoen er signifikant høyere enn uten antidepressiver. Ett års mortalitet (alle årsaker) var 7.04 % for pasienter som ikke tok antidepressiver, 8.12 % for pasienter som brukte TCA, 10,61 % for SSRI og 11.43 % for andre antidepressiver. I SoF-tabellen er kun SSRI-mortalitet gitt ved HR oppgitt.
Antidepressiver har også andre kjente bivirkninger, som er relativt vanlige.

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE					ADDITIONAL CONSIDERATIONS
			year, events recorded in electronic medical record[13]					
			Falls (SSRIs vs no ADs) Events recorded in electronic medical record, rates per patient-year	204007 (1 study) 1-12 years	⊕⊕⊖⊖ **LOW**[15]	**HR 1.66** (1.58 to 1.73)	**61 per 1000 patient-years**[16]	**38 more per 1000 patient-years** (from 34 more to 42 more)

CI: Confidence interval; **OR:** Odds ratio; **HR:** Hazard ratio;

[1] The National Institute for Clinical Excellence (NICE) of the National Health Service in England has defined a threshold for clinical significance as an effect size of 0.50 or a drug/placebo difference of 3 points on the HDRS. Fournier et al estimated that this threshold was met for intake HDRS scores of 25 or greater, using the more liberal of the 2 criteria (a difference in HDRS scores of ≥3 points). The results are similar to previous reviews based on data from FDA, analysed on group level (Kirsch et al Plos Med 2008, Khan et al J Clin Psychopharmacol. 2002.)
[2] Fournier JAMA 2010: Metaanalysis of studies with individual data available for analysis. Five studies on major depressive disorder, one study on minor depression. Medication used: paroxetine in three studies, imipramin in three studies.
[3] Percentages only reported, not number of participants
[4] Selective publication of positive AD trials has been reported by Turner et al in NEJM 2008, inflating the effect size of ADs in SRs.
[5] 12 adult and 4 geriatric studies of fluoxetine hydrochloride, and 21 adult studies of venlafaxine hydrochloride.
[6] Risk of bias of included studies not thoroughly reported, studies being double blinded RCTs with individual data available, and information about baseline HDRS score
[7] Studies on adults with depression, not only elderly, not only patients with mild depression.
[8] No effect of baseline severity on treatment efficacy was found for either the dichotomous (P=.27) or continuous (P=.10) baseline severity measures. For patients with low severity, the rates of change in symptoms over 6 weeks were −9.40HAM-Dunits for drug vs −7.20HAM-Dunits for placebo. For patients with high severity, the rates of change were −12.85 for drug vs −10.07 for placebo. The estimated differences were 2.20 HAM-D units (95% CI, 1.65- 2.76) for low severity and 2.78HAM-Dunits (95% CI, 2.26-3.29) for high severity.
[9] All studies on fluoxetein (12 adult+4 geriatric studies) and venlafaxin (21 adult studies)
[10] Four geriatric studies on fluoxetine
[11] Wide CI crossing no difference
[12] marginal maximum likelihood estimate (MMLE) and standard error of the difference in HAM-D

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
			reported, MMLE=−1.39; SE=0.50; P=.009), indicating 18.5% greater improvement for fluoxetine. Confidence interval not reported. [13] Adjusted for sex, age (five year bands), year, severity of depression, depression before age 65, smoking status, Townsend deprivation score, coronary heart disease, diabetes, hypertension, cancer, dementia, Parkinson's disease, hypothyroidism, obsessive-compulsive disorder, epilepsy/seizures, statins, non-steroidal anti-inflammatory drugs, antipsychotics, lithium, aspirin, antihypertensive drugs, anticonvulsant drugs, hypnotics/anxiolytics; and stroke/transient ischaemic attack at baseline. [14] The control rate are patients not currently on ADs [15] This is a well done large observational study based on a primary care database from 570 general practices in UK. As this is an observational study, it is susceptible to confounding by indication, channelling bias, and residual confounding, so differences in characteristics between patients prescribed different antidepressant drugs that could account for some of the associations between the drugs and the adverse outcomes may remain. We decided not to downgrade further, however. [16] The rate is calculated by total numbers of event divided by person year, and indicates event rate per person-year Link to detailed evidence profile **Subgroup considerations:** Effekten av behandling av milde depresjoner hos pasienter som tidligere har hatt nytte av antidepressiver ved depressive episode er ikke godt dokumentert, og er først og fremst basert på klinisk skjønn.	

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
RESOURCE USE	**Are the resources required small?**	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☒ *Yes* ☐ ***Varies*** ☐		Pasienter med mild depresjon kan ha nytte av andre rimelige lav-intensitetstiltak som rådgivning og selvhjelp.
	Is the incremental cost small relative to the net benefits?	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☒ *Yes* ☐ ***Varies*** ☐		Vi antar at det er kostandseffektivt å ikke behandle elder med mild depresjon med antidepressiver, men heller velge andre tiltak som rådgivning og selvhjelp.

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
EQUITY	**What would be the impact on health inequities?**	*Increased* ☐ *Probably increased* ☐ *Uncertain* ☒ *Probably reduced* ☐ *Reduced* ☐ ***Varies*** ☐		Sannsynligvis ingen innvirkning på social ulikhet.
ACCEPTABILITY	**Is the option acceptable to key stakeholders?**	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ ***Varies*** ☐		Referansegruppen har drøftet og støtter anbefalingen om ikke å behandle mild depresjon med antidepressiver. Vi tror at informerte pasienter også vil finne at dette er akseptabelt. Anbefalingen åpner for at antidepressiver kan brukes i enkelte tilfeller.
FEASIBILITY	**Is the option feasible to implement?**	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ ***Varies*** ☐		Ja.

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings	Undesirable consequences *probably outweigh* desirable consequences in most settings	The balance between desirable and undesirable consequences *is closely balanced or uncertain*	Desirable consequences *probably outweigh* undesirable consequences in most settings	Desirable consequences *clearly outweigh* undesirable consequences in most settings
	☐	☒	☐	☐	☐

Type of recommendation	We recommend against offering this option	We suggest not offering this option	We suggest offering this option	We recommend offering this option
	☒	☐	☐	☐

Recommendation (text)

Vi anbefaler:

Mild depresjon

Fastleger bør vanligvis ikke forskrive antidepressive legemidler ved milde depresjoner.

- **Fastleger kan vurdere å gi antidepressive legemidler ved milde depresjoner til pasienter som tidligere har hatt moderat til alvorlige depresjoner med god effekt av slike legemidler.**

Justification

Det er dokumentasjon av moderat kvalitet for at pasienter med mild depresjon har liten nytte av antidepressive legemidler. Antidepressiver har flere kjente bivirkninger, og vi har dokumentasjon av lav kvalitet for at antidepressiver til eldre med depresjon gir økt mortalitet og økt risiko for fall. Vi mangler dokumentasjon for at pasienter som tidligere har hatt moderat til alvorlige depresjoner har effekt av antidepressiv behandling ved milde depresjoner. Antidepressive legemidler har bivirkninger, og mange pasienter ønsker å slippe å bruke medisiner, mens andre ønsker å forsøke medikamentell behandling. Anbefalingen er derfor sterk for at antidepressive legemidler ikke skal forskrives ved milde depresjoner, og svak for at pasienter med tidligere moderat til alvorlig depresjon bør få antidepressiver.

Vår vurdering er at de nyttige effektene av antidepressiver ved mild depresjon hos eldre ikke oppveier bivirkningene. En mild depresjon er en lite alvorlig tilstand, der vi har andre mer effektive tiltak enn antidepressiver. Det er risiko for at oppstart medikamentell behandling vil redusere sannsynligheten for at andre tiltak iverksettes.

Subgroup considerations

Antidepressiver kan vurderes hos eldre med mild depresjon som har hatt effekt av medikamenter ved tidligere depresjoner eller som har tilbakevendende depresjon, kronisk depresjon eller dystymi. Denne delen av anbefalingen er gitt på kliniske grunnlag, og vi har ikke funnet systematiske oversikter som støtter anbefalingen.

Implementation considerations

Monitoring and evaluation

Research priorities

Evidence profile Antidepressiver ved mild depresjon hos eldre

Author(s): [Authors]
Date: [YYYY-MM-DD]

Author(s): Signe Flottorp, Eivind Aakhus, Ingeborg Granlund
Date: 2013-08-13
Question: Should antidepressants be used for elderly with mild depression?
Settings: Primary care
Bibliography: Adult population: Fournier JC et al. Antidepressant Drug Effects and Depression Severity. JAMA 2010. Geriatric population: Gibbons et al. Benefits from antidepressants: synthesis of 6-week patient-level outcomes from double-blind placebo-controlled randomized trials of fluoxetine and venlafaxine. Arch Gen Psychiatry 2012.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antidepressants	Control	Relative (95% CI)	Absolute		
Symptom change in patients with mild to moderate depression (baseline HDRS 18 or less) (follow-up 6-11 weeks; measured with: Hamilton Depression Rating Scale (HDRS); Better indicated by lower values)												
6[1]	randomised trials	no serious risk of bias[2]	no serious inconsistency	no serious indirectness[3]	serious[4]	none[5]	-	-	SMD 0.11 lower (0.41 lower to 0.18 higher)[6]		⊕⊕⊕◯ MODERATE	CRITICAL
Response rate (assessed with: Hamilton Depression rating scale (HDRS))												
16[7]	randomised trials	no serious risk of bias[2]	no serious inconsistency	serious[3]	no serious imprecision	reporting bias[8]	584/1000 (58.4%)[9]	399/1000 (39.9%)[9]	OR 2.11 (1.93 to 2.31)[8]	184 more per 1000 (from 163 more to 206 more)	⊕⊕◯◯ LOW	CRITICAL[10]
Remission rates (follow-up mean 6 weeks; assessed with: HDRS)												
37[11]	randomised trials	no serious risk of bias[2]	no serious inconsistency	serious[3]	no serious imprecision	reporting bias[8]	430/1000 (43%)[9]	293/1000 (29.3%)[9]	OR 1.82 (1.66 to 2)[8,12]	137 more per 1000 (from 115 more to 160 more)	⊕⊕◯◯ LOW	CRITICAL[13]
Response rate - geriatric studies only (follow-up mean 6 weeks; assessed with: HDRS)												
4[14]	randomised trials	no serious risk of bias[2]	no serious inconsistency	no serious indirectness	serious[4]	reporting bias[8]	373/1000 (37.3%)[9]	274/1000 (27.4%)[9]	OR 1.42 (0.92 to 2.18)	75 more per 1000 (from 16 fewer to 177 more)	⊕⊕◯◯ LOW	CRITICAL
Remission rates - geriatric studies (follow-up mean 6 weeks; assessed with: HDRS)												
4[14]	randomised trials	no serious risk of bias[2]	no serious inconsistency	no serious indirectness	serious[4]	reporting bias[8]	265/1000 (26.5%)[9]	200/1000 (20%)[9]	OR 1.26 (0.78 to 2.03)	40 more per 1000 (from 37 fewer to 137 more)	⊕⊕◯◯ LOW	CRITICAL
Depressive symptoms - geriatric studies mild depression (follow-up mean 6 weeks; measured with: HDRS; Better indicated by lower values)												
4[14]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	mean HDRS score 6.89 lower	mean HDRS score .5.42 lower	mean HDSR 1.47 lower (3.20 lower to 0.26 higher)[15]		⊕⊕⊕◯ MODERATE	CRITICAL

All cause mortality (SSRI vs no ADs) (follow-up 1-12 years; assessed with: Number of events per patient-year - measured with electronic medical record database[16])												
1	observational studies	no serious risk of bias[17]	no serious inconsistency	no serious indirectness	no serious imprecision	none	5782/70893 (8.2%)[18]	8210/170864 (4.8%)[19]	HR 1.54 (1.48 to 1.59)[16]	25 more per 1000 (from 22 more to 27 more)	⊕⊕◯◯ LOW	CRITICAL
Falls (SSRIs vs no ADs) (follow-up 1-12 years; assessed with: Events recorded in electronic medical record, rates per patient-year)												
1	observational studies	no serious risk of bias[17]	no serious inconsistency	no serious indirectness	no serious imprecision	none	5208/145407 (3.6%)[18]	3575/58600 (6.1%)[18]	HR 1.66 (1.58 to 1.73)	38 more per 1000 (from 34 more to 42 more)	⊕⊕◯◯ LOW	IMPORTANT

[1] Fournier JAMA 2010: Metaanalysis of studies with individual data available for analysis. Five studies on major depressive disorder, one study on minor depression. Medication used: paroxetine in three studies, imipramin in three studies.

[2] Risk of bias of included studies not thoroughly reported, studies being double blinded RCTs wit individual data available, and information about baseline HDRS score

[3] Studies on adults with depression, not only elderly, not only patients with mild depression.

[4] Wide CI crossing no difference

[5] Few studies in the literature report the magnitude of the baseline severity × treatment interaction effect, publication bias difficult to assess. Selective publication of positive AD trials has been reported by Turner et al in NEJM 2008, inflating the effect size of ADs in SRs. Since our recommendation is to not treat mild depression with AD, we do not downgrade because of reporting bias: the effect of ADs in patients with mild depression is likely to be less than effect reported in published studies.

[6] The National Institute for Clinical Excellence (NICE) of the National Health Service in England has defined a threshold for clinical significance as an effect size of 0.50 or a drug/placebo difference of 3 points on the HDRS. Fournier et al estimated that this threshold was met for intake HDRS scores of 25 or greater, using the more liberal of the 2 criteria (a difference in HDRS scores of ≥3 points). The results are similar to previous reviews based on data from FDA, analysed on group level (Kirsch et al Plos Med 2008, Khan et al J Clin Psychopharmacol. 2002.)

[7] 12 adult and 4 geriatric studies of fluoxetine hydrochloride, and 21 adult studies of venlafaxine hydrochloride.

[8] Selective publication of positive AD trials has been reported by Turner et al in NEJM 2008, inflating the effect size of ADs in SRs.

[9] Percentages only reported, not number of participants

[10] Response was a 50% reduction in the HAM-D score at week 6

[11] All studies on fluoxetin (12 adult+4 geriatric studies) and venlafaxin (21 adult studies)

[12] No effect of baseline severity on treatment efficacy was found for either the dichotomous (P=.27) or continuous (P=.10) baseline severity measures. For patients with low severity, the rates of change in symptoms over 6 weeks were −9.40HAM-Dunits for drug vs −7.20HAM-Dunits for placebo. For patients with high severity, the rates of change were −12.85 for drug vs −10.07 for placebo. The estimated differences were 2.20 HAM-D units (95% CI, 1.65- 2.76) for low severity and 2.78HAM-Dunits (95% CI, 2.26-3.29) for high severity.

[13] remission was a HAM-D score lower than 8 at week 6.

[14] Four geriatric studies on fluoxetine

[15] marginal maximum likelihood estimate (MMLE) and standard error of the difference in HAM-D reported, MMLE=−1.39; SE=0.50; P=.009), indicating 18.5% greater improvement for fluoxetine. Confidence interval not reported.

[16] Adjusted for sex, age (five year bands), year, severity of depression, depression before age 65, smoking status, Townsend deprivation score, coronary heart disease, diabetes, hypertension, cancer, dementia, Parkinson's disease, hypothyroidism, obsessive-compulsive disorder, epilepsy/seizures, statins, non-steroidal anti-inflammatory drugs, antipsychotics, lithium, aspirin, antihypertensive drugs, anticonvulsant drugs, hypnotics/anxiolytics; and stroke/transient ischaemic attack at baseline.

[17] This is a well done large observational study based on a primary care database from 570 general practices in UK. As this is an observational study, it is susceptible to confounding by indication, channelling bias, and residual confounding, so differences in characteristics between patients prescribed different antidepressant drugs that could account for some of the associations between the drugs and the adverse outcomes may remain. We decided not to downgrade further, however.

[18] The rate is calculated by total numbers of event divided by person year, and indicates event rate per person-year

[19] The control rate are patients not currently on ADs

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References

[1] Fournier JC et al. Antidepressant drug effects and depression severity. JAMA: The Journal of the American Medical Association 2010;303:47-53.

[2] Gibbons RD et al. Benefits from antidepressants: synthesis of 6-week patient-level outcomes from double-blind placebo-controlled randomized trials of fluoxetine and venlafaxine. Arch Gen Psychiatry 2012;69:572-9.

[3] Coupland C et al. Antidepressant use and risk of adverse outcomes in older people: population based cohort study. BMJ 2011;343:d4551.

Definitions for ratings of the certainty of the evidence (GRADE)**

Ratings	Definitions	Implications
⨁⨁⨁⨁ High	This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different* is low.	This evidence provides a very good basis for making a decision about whether to implement the intervention. Impact evaluation and monitoring of the impact are unlikely to be needed if it is implemented.
⨁⨁⨁◯ Moderate	This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different[4] is moderate.	This evidence provides a good basis for making a decision about whether to implement the intervention. Monitoring of the impact is likely to be needed and impact evaluation may be warranted if it is implemented.
⨁⨁◯◯ Low	This research provides some indication of the likely effect. However, the likelihood that it will be substantially different[4] is high.	This evidence provides some basis for making a decision about whether to implement the intervention. Impact evaluation is likely to be warranted if it is implemented.
⨁◯◯◯ Very low	This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different[4] is very high.	This evidence does not provide a good basis for making a decision about whether to implement the intervention. Impact evaluation is very likely to be warranted if it is implemented.

*Substantially different: large enough difference that it might have an effect on a decision

**The Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group began in the year 2000 as an informal collaboration of people with an interest in addressing the shortcomings of present grading systems in health care. The working group has developed a common, sensible and transparent approach to grading quality of evidence and strength of recommendations. Many international organizations have provided input into the development of the approach and have started using it.

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