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Salmeterol and Fluticasone Propionate and Survival in Chronic Obstructive Pulmonary Disease

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Calverley et al. (2007) Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med 356:775-789.

Salmeterol 50 mikrogram x 2
Flutikasonpropionat 500 mikrogram x 2
3 år behandling

Inklussionskriterier

PATIENTS

We recruited patients who were current or former smokers with at least a 10-pack-year history. Eligible patients were 40 to 80 years of age and had received a diagnosis of COPD, with a prebronchodilator forced expiratory volume in 1 second (FEV_1) of less than 60% of the predicted value,[15] an increase of FEV_1 with the use of 400 μg of albuterol of less than 10% of the predicted value for that patient, and a ratio of prebronchodilator FEV_1 to forced vital capacity (FVC) equal to or less than 0.70.

Studiepopulation

Table 1. Demographic and Baseline Clinical Characteristics of Patients in the Efficacy Population.*

Medelvärden±standardavvikelse, SD

Variable	Placebo Group (N=1524)	Salmeterol Group (N=1521)	Fluticasone Group (N=1534)	Combination-Therapy Group (N=1533)
Age at enrollment — yr	65.0±8.2	65.1±8.2	65.0±8.4	65.0±8.3
Male sex — no. (%)	1163 (76)	1160 (76)	1157 (75)	1151 (75)
Body-mass index†	25.4±5.2	25.4±5.2	25.4±5.1	25.4±5.3
Geographic region — no. (%)				
United States	345 (23)	346 (23)	348 (23)	349 (23)
Asia–Pacific	188 (12)	189 (12)	193 (13)	188 (12)
Eastern Europe	290 (19)	289 (19)	287 (19)	288 (19)
Western Europe	476 (31)	475 (31)	481 (31)	476 (31)
Other	225 (15)	222 (15)	225 (15)	232 (15)
Current smoker — no. (%)	658 (43)	651 (43)	661 (43)	660 (43)
Pack-years — no.	48.6±26.9	49.3±27.7	49.2±28.6	47.0±26.5
Previous treatment — no. (%)‡				
Inhaled corticosteroid	338 (22)	273 (18)	306 (20)	292 (19)
Long-acting beta-agonist	118 (8)	137 (9)	130 (8)	137 (9)
Inhaled corticosteroid plus long-acting beta-agonist	449 (29)	413 (27)	414 (27)	435 (28)
Exacerbation — no.‡				
Requiring antibiotics or oral corticosteroids	1.0±1.4	1.0±1.4	1.0±1.4	1.0±1.3
Requiring hospitalization	0.2±0.7	0.2±0.6	0.2±0.6	0.2±0.6

Studiepopulation

Pack-years (95% konfidensintervall, CI):

Placebo (n=1524): 48.6 (95% CI 47.2-50.0)
Komb. beh. (n=1533): 47.0 (95% CI 45.7-48.3)

t-test:
Skillnad 1.600 (95% CI -0.298 to 3.498)
p=0.0977

Hur sjuka var patienterna?

Lung function§				
Prebronchodilator FEV_1 — liters	1.12±0.40	1.10±0.39	1.12±0.39	1.12±0.40
Postbronchodilator FEV_1 — liters	1.22±0.42	1.21±0.41	1.22±0.41	1.22±0.42
FEV_1 — % of predicted	44.1±12.3	43.6±12.6	44.1±12.3	44.3±12.3
Reversibility — % of predicted FEV_1¶	3.7±3.7	3.7±3.9	3.7±3.7	3.6±3.6
Prebronchodilator FEV_1:FVC (%)	48.6±10.9	48.7±10.8	48.5±10.7	48.7±10.8
Total score at baseline on St. George's Respiratory Questionnaire‖	49.0±17.4	49.9±16.6	49.5±17.1	48.9±17.4

KOL/FEV_1 (efter bronkdilatation):
Preklinisk KOL: FEV_1 >80% av förväntat värde
Lindrig KOL: FEV_1 50-79% av förväntat värde
Medelsvår KOL: FEV_1 30-49% av förväntat värde
Svår KOL: FEV_1 <30% av förväntat värde

Ställberg B & Skoogh BE (2007) Läkartidningen 104(13):1036-9.

Primär utfallsvariabel

Primary endpoint was death from any cause by 3 years.

Table 2. Results of the Mortality Analysis and the Efficacy Analysis for Exacerbation.

Variable	Placebo Group (N=1524)	Salmeterol Group (N=1521)	Fluticasone Group (N=1534)	Combination-Therapy Group (N=1533)	Comparison	Hazard Ratio (95% CI)	P Value
Mortality analysis							
No. of deaths from any cause	231	205	246	193			
Probability of death at 3 yr — %	15.2	13.5	16.0	12.6	Combination therapy vs. placebo (adjusted)*	0.825 (0.681–1.002)	0.052

There were 875 deaths within 3 years after randomization. The proportions of deaths from any cause at 3 years were 12.6% in the combination-therapy group, 15.2% in the placebo group, 13.5% in the salmeterol group, and 16.0% in the fluticasone group. The absolute risk reduction for death in the combination-therapy group as compared with the placebo group was 2.6%, and the hazard ratio was 0.825 (95% confidence interval [CI], 0.681 to 1.002; P=0.052), corresponding to a reduction in the risk of death at any time in the 3 years of 17.5% (95% CI, −0.2 to 31.9) (all adjusted for the interim analyses) (Fig. 2B and Table 2).

Diskussion

There are two possible reasons why the reduction in mortality in the combination-therapy group, as compared with the placebo group, did not achieve statistical significance. The first is that there is no effect of salmeterol plus fluticasone propionate on survival.

The second possible reason, which we believe is the more likely one, is that salmeterol plus fluticasone propionate does have an effect on mortality but that our study was underpowered to detect this effect.

Studiens power

Blev 15.2%

STATISTICAL ANALYSIS

All reported data analyses were prespecified. Assuming a 17% mortality rate in the placebo group at 3 years,[17] we estimated that 1510 patients would be needed for each study group to detect a reduction in mortality of 4.3 percentage points in the combination-therapy group, as compared with the placebo group (hazard ratio for death, 0.728), at a two-sided alpha level of 0.05 with 90% power.

Blev 2.6%

Blev 0.825

Studiens power (styrka)

Resultat av hypotesprövning	"Sanningen"	
	H_0 falsk	H_0 sann
H_0 förkastas (sannolikhet)	OK (1-beta, power, vanligen 0,8-0,9)	Typ I fel (alfa, vanligen 0,05)
H_0 accepteras (sannolikhet)	Typ II fel (beta)	OK (1-alfa)

H_0 = nollhypotes, vanligen att det inte finns någon skillnad mellan grupperna som jämförs.
Typ I-fel (sannolikhet alfa):
Förkasta nollhypotesen trots att den är sann.
Typ II-fel (sannolikhet beta):
Acceptera nollhypotesen trots att den är falsk.
Power (sannolikhet 1-beta): sannolikheten att korrekt förkasta en falsk nollhypotes.

Relativ risk/Absolut risk/NNT

sone group. The absolute risk reduction for death in the combination-therapy group as compared with the placebo group was 2.6%, and the hazard ratio was 0.825 (95% confidence interval [CI], 0.681 to 1.002; P=0.052), corresponding to a reduction in the risk of death at any time in the 3 years of 17.5% (95% CI, −0.2 to 31.9) (all adjusted for

Relativ riskreduktion (RRR) = 17.5%
Absolut riskreduktion (ARR) = 2.6% (0.026)
NNT = 1/ARR = 1/0.026 = 38.5. Om 38.5 personer behandlas med kombinationsbehandlingen i tre år kommer ytterligare en att överleva. MEN ingen statistisk signifikans så det återstår en osäkerhet om det verkligen finns en skillnad mellan behandlade och kontroller.

NNT-tal

NNT-talet vi beräknade blev 38.5. Vilket är det bästa NNT-tal som skulle kunna erhållas i studien?

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Absolut risk att dö under de tre åren i placebogruppen är 15.2%. Om alla dessa dödsfall kunde förhindras blir absolut riskreduktion (ARR) 15.2%=0.152.

NNT=1/ARR=1/0.152=6.6

Primär utfallsvariabel

Primary endpoint was death from any cause by 3 years.

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					Combination therapy vs. placebo (unadjusted)	0.820 (0.677–0.993)	0.04

two interim efficacy analyses were performed, the first after the first 358 deaths had occurred and the second after a total of 680 deaths had occurred.

Interimanalyser

Two interim analyses of death from any cause were planned to assess whether there was overwhelming evidence of a benefit from the combination regimen, as compared with placebo, or of harm in any study group; these analyses were performed by the independent safety and efficacy data monitoring committee according to the method of Whitehead.[18] As a consequence, the P value for the primary comparison between the combination regimen and placebo was adjusted upward to conserve an overall significance level of 0.050.

Interimanalyser

Varje gång resultaten analyseras riskerar man att göra ett typ I fel. Analyserar man tre gånger (två interim och en slutlig) med alfa=0.05 vid varje analys blir den sammanlagda risken att göra ett typ I fel betydligt större än 0.05. För att bevara alfa=0.05 för den sammanlagda risken att göra ett typ I fel i studien fördelas alfa på de olika analyserna (alpha spending). Om alfa=0.05 för hela studien blir det alfa man kan använda för statistisk signifikans i den slutliga analysen lägre än 0.05.

Primär utfallsvariabel

Table 2. Results of the Mortality Analysis and the Efficacy Analysis for Exacerbation.

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Absolut risk/Relativ risk

LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Occurrence of narcolepsy with cataplexy among children and adolescents in relation to the H1N1 pandemic and Pandemrix vaccinations
- Results of a case inventory study by the MPA in Sweden during 2009-2010

The incidence rates were measured to be 4.2 per 100 000 in the vaccinated cohort, compared to 0.64 per 100 000 in the non-vaccinated cohort, yielding a relative risk of 6.6 (95% CI 3.1-14.5) and an absolute risk of 3.6 additional cases per 100 000 vaccinated subjects.

Relativ riskökning 6.6x
Absolut riskökning 3.6/100 000 = 1/27778
NNH (number needed to harm) = 27778

Om 27778 individer vaccineras kommer en att drabbas av narkolepsi.

Ovanliga biverkningar

Hur många individer behöver studeras för att med 95% sannolikhet upptäcka en biverkning som förekommer hos 1 av 27778?

Enligt ”rule of 3” behöver man studera 3x27778, dvs 83334.

Sannolikheten att inte drabbas är 1-1/27778 för varje individ. Sannolikheten att ingen av 83334 individer drabbas är $(1-1/27778)^{83334}=0.0498$

Ovanliga biverkningar

Vad kan man säga om risken för en biverkning som inte observerats i en klinisk prövning med 3000 exponerade (behandlade) individer?

Enligt ”rule of 3” är risken för en sådan biverkning med 95% sannolikhet < 1/1000.

Publikationer/Statistik

Efficacy and safety of vortioxetine (Lu AA21004), 15 and 20 mg/day: a randomized, double-blind, placebo-controlled, duloxetine-referenced study in the acute treatment of adult patients with major depressive disorder

Jean-Philippe Boulenger[a], Henrik Loft[b] and Christina Kurre Olsen[b]

Int Clin Psychopharmacol., 2014, 29:138-149.

Vortioxetin (Brintellix)

Inklusionskriterier

Main entry criteria

Patients aged at least 18 and up to 75 years, with a primary diagnosis of recurrent MDD according to *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed., text revision (DSM-IV-TR) criteria (American Psychiatric Association (APA), 2000), a current major depressive episode (MDE) of greater than 3 months' duration with an MADRS total score of at least 26 and a Clinical Global Impression – Severity (CGI-S) (Guy, 1976) score of at least 4 at screening and baseline visits were eligible for inclusion in the study.

Exklusionskriterier

Patients were excluded if they had any current psychiatric disorder other than MDD as defined in the DSM-IV-TR, or a current or past history of a manic or hypomanic episode, schizophrenia or any other psychotic disorder, mental retardation, organic mental disorders or mental disorders due to a general medical condition, any current diagnosis of substance abuse or dependence as defined in DSM-IV-TR, the presence or history of a clinically significant neurological disorder, or any neurodegenerative disorder that might compromise their participation in the study.

Exklusionskriterier

Patients at serious risk of suicide, on the basis of the investigator's clinical judgement, or those who had a score of at least 5 on item 10 of the MADRS scale ('suicidal thoughts') were excluded, as were those receiving formal psychological treatments; pregnant or breast-feeding women; those with current depressive symptoms considered by the investigator to have been resistant to two adequate antidepressant treatments of at least 6-week duration; those who had failed to respond to treatment with duloxetine, or who had proved hypersensitive to duloxetine; and those who had previously been exposed to vortioxetine. Patients were also excluded if they were taking disallowed concomitant medication, as described by Alvarez *et al.* (2012), as well as the antibiotics rifampicin and ciprofloxacin, although antiarrhythmics, antihypertensives (except metoprolol, carvedilol, timolol and Class 1C antiarrhythmics) and proton pump inhibitors (except omeprazole and cimetidine) were permitted. Episodic use of zolpidem, zopiclone or zaleplon for severe insomnia was allowed for a maximum of 2 days/week, but not the night before a study visit.

Exklusionskriterier

Patients were also excluded if they had a clinically significant unstable illness, a thyroid-stimulating hormone value outside the reference range, history of cancer in remission for less than 5 years, clinically significant abnormal vital signs as determined by the investigator, an abnormal ECG at screening considered by the investigator to be clinically significant, or a PR interval > 250 ms, a QRS interval > 130 ms or a QTcF interval > 450 ms (for men) or >470 ms (for women).

Inklussions- och exklussionskriterier avgör hur generaliserbara studiens resultat är.

Hur sjuka var patienterna?

Table 1 Baseline patient characteristics

	Placebo ($n=158$)	Vortioxetine 15 mg ($n=151$)	Vortioxetine 20 mg ($n=151$)
APTS			
Women [n (%)]	110 (69.6)	97 (64.2)	91 (60.3)
Age (mean±SD)	48.1±13.1	47.0±14.6	46.2±13.4
Range (years)	21–74	18–74	18–73
Caucasian (%)	98.7	99.3	96.7
Median length of current MDE (weeks)	24	21	22
Previous MDEs±SD	2.0±1.4	2.1±1.5	1.8±1.3
Range	1–8	1–11	1–7
Rating scale scores (FAS)	$n=158$	$n=149$	$n=151$
MADRS total score±SD	31.5±3.6	31.8±3.4	31.2±3.4
HAM-A total score±SD	20.8±6.6	21.3±6.8	20.4±6.9
CGI-S±SD	4.9±0.7	4.9±0.6	4.8±0.7
Q-LES-Q total score±SD	34.1±7.0	33.2±7.0	33.7±7.2
SDS social±SD	6.8±2.1	6.9±2.0	6.8±2.0
SDS family±SD	6.9±2.1	6.7±2.2	7.0±1.9
	$n=115$	$n=97$	$n=107$
SDS work±SD	6.3±2.8	6.8±2.1	6.9±2.0
SDS total±SD	19.8±6.0	20.6±5.3	20.7±4.8

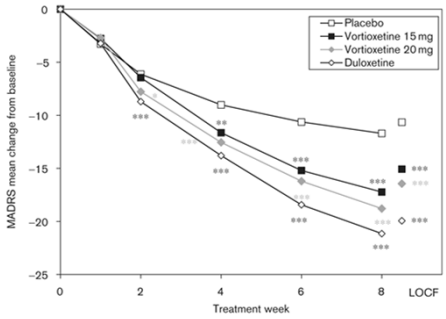
MADRS: 15–20 lindriga depressionssymtom; 21–30 måttliga depressionssymtom; >30 svåra depressionssymtom

https://lakemedelsboken.se/kapitel/psykiatri/forstamningssyndrom.html#facts_1_header

Utfallsvariabler (endpoints)

(1) change from baseline in MADRS total score (primary);
(2) response (defined as a $\geq$ 50% decrease from baseline in MADRS total score);
(3) Clinical Global Impression – Improvement scale (CGI-I) score;
(4) change from baseline in MADRS total score in patients with a baseline HAM-A total score of at least 20;
(5) remission (defined as an MADRS total score $\leq$ 10);
(6) change from baseline in SDS total score.

Hur friska blev patienterna?



LOCF: last observation carried forward. Man tar med resultat även från studiedeltagare som hoppar av studien.

Hur friska blev patienterna?

Table 2 Efficacy analyses, change from baseline to week 8 (FAS, MMRM)

	Placebo	Vortioxetine 15 mg		Vortioxetine 20 mg	
	Δ Baseline	Δ Baseline	*P*-value	Δ Baseline	*P*-value
Primary efficacy variable					
Δ MADRS total score	−11.7	−17.2	<0.0001	−18.8	<0.0001
Key secondary efficacy variables					
MADRS response[a]	32.3%	57.0%	<0.0001	61.6%	<0.0001
CGI-I score[b]	2.86	2.18	<0.0001	1.92	<0.0001
Δ MADRS total score (HAM-A ≥ 20)[c]	−12.2	−17.4	0.0007	−18.6	<0.0001
MADRS remission[a]	19.0%	34.9%	0.0016	38.4%	0.0002
Δ SDS total score	−4.5	−7.7	0.0054	−8.4	0.0005
Secondary efficacy variables					
Q-LES-Q total score (LOCF, ANCOVA)	5.2	3.3	0.0020	4.5	<0.0001
SDS work subscale	−1.4	−2.4	0.0246	−2.6	0.0059
SDS social life subscale	−1.7	−2.7	0.0006	−3.1	<0.0001
SDS family life subscale	−1.7	−2.8	0.0002	−3.1	<0.0001
Δ CGI-S score	−1.3	−2.1	<0.0001	−2.4	<0.0001
Δ HAM-A	−7.1	−9.6	0.0012	−11.1	<0.0001
CGI-I ≤ 2 (response)[a]	38.0%	63.1%	<0.0001	70.2%	<0.0001
CGI-S ≤ 2 (remission)[a]	21.5%	40.9%	0.0003	45.0%	<0.0001

MADRS remission (≤ 10):
Placebo 19.0%, Vortioxetin 20 mg 38.4%

Hur friska blev patienterna?

MADRS remission (≤ 10):
Placebo 19.0% (81.0% fortsatt sjuka)
Vortioxetin 20 mg 38.4% (61.6% fortsatt sjuka)

Absolut riskreduktion (ARR)=
81.0%-61.6%=19.4%=0.194

Number needed to treat (NNT)=1/ARR=1/0.194=5.2

5.2 personer måste behandlas för att ytterligare en ska bli frisk (en hade blivit frisk utan läkemedel, tre är fortsatt sjuka).

Biverkningar

Table 3 Adverse events with an incidence of ≥ 5% in any treatment group in the 8-week treatment period (APTS)

	n (%)		
Preferred term	Placebo (*n* = 158)	Vortioxetine 15 mg (*n* = 151)	Vortioxetine 20 mg (*n* = 151)
Patients with TEAEs	80 (50.6)	86 (57.0)	100 (66.2)
Nausea	16 (10.1)	40 (26.5)***	48 (31.8)***
Headache	12 (7.6)	16 (10.6)	19 (12.6)
Diarrhea	6 (3.8)	6 (4.0)	11 (7.3)
Dry mouth	5 (3.2)	5 (3.3)	9 (6.0)
Dizziness	10 (6.4)	7 (4.6)	8 (5.3)
Fatigue	4 (2.5)	6 (4.0)	5 (3.3)
Hyperhidrosis	6 (3.8)	5 (3.3)	0 (0.0)

APTS, all-patients-treated set; TEAEs, treatment-emergent adverse events.
*P<0.05.
***P<0.001 versus placebo.

Flertalet kliniska prövningar har inte så stort antal deltagare att sällsynta biverkningar upptäcks. Viktigt med biverkningsuppföljning efter att nya läkemedel registrerats.