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Bibliographic Data	
Authors	Gilron I, Tu D, et al.
Title	Combination of morphine with nortriptyline for neuropathic pain.
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Other information if relevant	

Methods	
Aim of study	In the setting of neuropathic pain, to compare the effectiveness of morphine monotherapy, nortriptyline monotherapy, and a combination of both drugs in the relief of pain
Design	Crossover randomized trial

Participants	
Population from which participants are drawn	Patients with neuropathic pain
Setting (location and type of facility)	A single anesthesiology department at Queen's University in Ontario
Age	66
Sex	38 men, 14 women
Total number of participants for whom outcome data were reported	52
Inclusion criteria	Age 18 to 89 with peripheral neuropathic pain and a score of 4 or more on the DN4 questionnaire for neuropathic pain symptoms, with sufficient cognitive function to participate in the study

Exclusion criteria	Pregnancy or lactation, elevated liver enzymes or creatinine, moderate to severe heart disease, cardiovasculare autonomic neuropathy, psychiatric or seizure disorder, taking MAO inhibitors, SSRI or SNRI; history of abuse of drugs or alcohol
Other information if relevant	The DN4 is a ten item questionnaire (Bouhassira et al 2005) in which the patient answers yes or no to characteristics such as burning, electric shock symptoms, tingling, numbness itching, etc; a score of 4 or more is considered to identify the pain as neuropathic in nature

Intervention Groups

Group 1	
Group name	MCN (morphine, nortriptyline, combination) sequence of administration
Number in group	17
Description of intervention	- All intervention periods were identical for all three groups, which were randomized to one of three sequences of treatment - In each period, patients received two sets of encapsulated medications, yellow (nortriptyline) or white (morphine), with yellow or white placebo capsules identical in appearance to the real drug - Patients took both yellow and white capsules each day, and were blinded as to the contents of the capsules - During each six week period, the first 24 days were spent titrating the study drug to a maximum tolerated dose, with starting doses of 10 mg for both nortriptyline and morphine - Days 25 to 31 of each period were when the maximum tolerated dose was being taken - Days 32 to 28 involved a 7 day taper of both capsules - Days 39 to 42 involved a complete washout in which no drug was taken - A research nurse contacted patients twice weekly to ask about adverse effects requiring dosing modifications
Duration of treatment period	Each treatment period lasted six weeks, and differed only with respect to which active treatment was being taken, morphine, nortriptyline, or the combination of both drugs
Co-interventions if reported	Patients taking pregabalin or gabapentin were allowed to continue taking these drugs All patients received oral docusate for constipation prophylaxis throughout the study and oral sennosides as needed for constipation

Additional information if relevant	The target dose ceilings were 100 mg of nortriptyline and 100 mg of morphine, provided that the patient tolerated titration to that level; otherwise, a lower maximum tolerated dose was taken from day 25 to 31 It appears that during the combination period, both drugs were being titrated at the same time

Group 2	
Group name	NMC
Number in group	17
Description of intervention	- Identical to MCN, except that the sequence of active drug was nortriptyline, then morphine, then the combination
Duration of treatment period	Identical to MCN
Co-interventions if reported	Identical to MCN
Additional information if relevant	

Group 3	
Group name	CNM
Number in group	18
Description of intervention	Identical to MCN and NMC, except that the sequence of active drug was combination, then nortriptyline, then morphine
Duration of treatment period	Identical to MCN and NMC
Co-interventions if reported	Same as MCN and NMC
Additional information if relevant	

Primary outcome	
Outcome name and criteria for definition	Pain intensity
Time points measured and/or reported	Average daily score during the period of ceiling medication dose, days 25 to 31

Differences between groups	Pain intensity measured as average daily pain was 3.4 for morphine monotherapy, 3.1 for nortriptyline monotherapy, and 2.6 for the combination; the difference between combination and monotherapy was statistically significant for both drug monotherapies The percentage of patients achieving a 50% reduction from baseline pain was 52.6% for the combination, 25.6% for morphine monotherapy, and 36.8% for nortriptyline monotherapy; the difference between combination and monotherapy was statistically significant for morphine but not for nortriptyline
Additional information if relevant	All crossover trials involve evaluation of sequence effects and carryover effects, which are distinguished from the main treatment effects of the study drug In the statistical analysis, neither sequence nor carryover effects were identified This means that the effect of nortriptyline monotherapy was the same for each group, whether they received it first, second, or third; the same is true for morphine monotherapy and for the nortriptyline/morphine combination The average ceiling dose for morphine monotherapy was 65.4 mg, and when taken in combination with nortriptyline, the mean ceiling dose was 60.2 mg The mean ceiling dose of nortriptyline monotherapy was 83.9 mg, versus 60.2 mg when taken in combination with morphine

Secondary outcomes	
Outcome name and criteria for definition	Numerous secondary endpoints were measured, of which adverse effects are the most relevant
Time points measured	During dose titration, at ceiling dose, and during dose taper
Differences between groups	During titration, dry mouth was more common with the combination (52%) than with nortriptyline monotherapy (29%) or morphine (17%) Constipation was rare during nortriptyline monotherapy (4%) but common during morphine monotherapy (49%) and combination (36%) Dizziness was more common with morphine (19%) than with nortriptyline (0%) Insomnia was common with nortriptyline monotherapy (13%) but not with morphine (0%) Diarrhea during taper washout occurred with morphine (10%) but not with nortriptyline (0%)
Additional information if relevant	Some unplanned subgroup analyses were done comparing the patients who were and those who were not taking pregabalin or gabapentin during the trial, but no clinically significant differences were found

Conclusions	
Key conclusions of study authors	- Combination therapy with morphine plus nortriptyline was more effective than monotherapy with either drug - The study also involved comparisons of monotherapy with morphine versus nortriptyline, where there was a nonsignificant trend in favor of nortriptyline over morphine for pain-related outcomes - Usually, clinical practice of combination therapy will not titrate both nortriptyline and placebo at the same time, but one drug will be added after the other drug has failed to provide adequate pain relief; this study does not replicate clinical practice in this respect

Risk of bias assessment		
Domain	Risk of bias Low High Unclear	Comments
Random sequence generation *(selection bias)*	Low	
Allocation concealment *(selection bias)*	Low	The allocation was done by a trial pharmacist who used a computer to randomize patients in blocks of 3 to the 3 different treatment sequences
Blinding of participants and personnel *(performance bias)*	Low	Both yellow and white capsules were taken by all patients throughout all three treatment sequences, and the placebo capsules were identical in appearance to the real capsules
Blinding of outcome assessment *(detection bias)*	Low	
Incomplete outcome data *(attrition bias)*	Low	Only one patient (in the NMC sequence) withdrew before starting; all other patients were included in the analysis

Selective outcome reporting? *(reporting bias)*	Low	The study protocol was available at the International Standard Randomized Controlled Trial Register, and the primary outcome in the report matched that in the protocol
Other bias		

Sponsorship if reported		
Study funding sources if reported	Canadian Institutes of Health Research supported the study; morphine was provided by Ethypharm, and nortriptyline was provided by Apotex Inc.	
Possible conflicts of interest for study authors	The first author has received support from various drug companies	
Notes:		

Comments by DOWC staff

- A generally well-done crossover study which made good use of the efficiencies inherent in that study design
- The description of the titration phase of the monotherapy treatments is clear enough, but the titration of the combination treatment is not
- That is, the titration phase involved increasing slowly from a starting dose to a ceiling dose, with a research nurse contacting patients twice per week for assessment of side effects and dose adjustment based on these symptoms
- When both nortriptyline and morphine were being titrated at the same time, it is not clear which drug would be adjusted when adverse events appeared
- It makes sense that if the patient had dry mouth during titration of combination treatment, the nurse would instruct the patient to take one less yellow capsule, and if the patient had dizziness, to take one less white capsule; however, this is not made explicit in either the article nor in the study protocol
- Although combination treatment was superior to monotherapy, the results suggest that more benefit would be derived from adding nortriptyline to morphine than would be derived from adding morphine to nortriptyline; due to the simultaneous titration of both drugs during the combination treatment period, this cannot be confirmed
- In a recent Cochrane review (McNicol 2013), monotherapy with an opioid was more effective in pain relief than a placebo, but was not superior to gabapentin or nortriptyline

Assessment by DOWC staff	

Overall assessment as suitability of evidence for the guideline ☐ High quality ☒ Adequate ☐ Inadequate	This study supports some evidence that in the setting of neuropathic pain, a combination of morphine plus nortriptyline produces better pain relief than either monotherapy alone, but morphine monotherapy is not superior to nortriptyline monotherapy, and it is possible that it is actually less effective than nortriptyline.
If inadequate, main reasons for recommending that the article not be cited as evidence	

Additional references if relevant
- McNicol ED, Midbari A, Eisenberg E. Opioids for neuropathic pain. Cochrane Database of Systematic Reviews 2013, Issue 8. Art. No.: CD006146.