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Best Evidence from the Cochrane Library

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Transtheoretical Model for Dietary and Physical Exercise Modification in Weight Loss Management for Overweight and Obese Adults

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Background: The Transtheoretical Model of Behavior Change assesses an individual's readiness to act on a new healthier behavior, and provides strategies, or processes of change to guide the individual through the stages of change to action and maintenance.

Obesity is a global public health threat. The transtheoretical model stages of change (TTM SOC) has long been considered a useful interventional approach in lifestyle modification programs, but its effectiveness in producing sustainable weight loss in overweight and obese individuals has been found to vary considerably.

Objective: To assess the effectiveness of dietary and physical activity interventions based on the transtheoretical model, to produce sustainable weight loss in overweight and obese adults.

Result: Five studies met the inclusion criteria and 3910 participants were evaluated. The total number of participants randomized to intervention groups was 1834 and 2076 were randomized to control groups. Overall risk of bias was high. The trials varied in length of intervention from six weeks to 24 months, with a median length of nine months. The intervention was found to have limited impact on weight loss (about 2 kg or less) and other outcome measures. There was no conclusive evidence for sustainable weight loss. However, TTM SOC and a combination of physical activity, diet and other interventions tended to produce significant outcomes (particularly change in physical activity and dietary intake). TTM SOC was used inconsistently as a theoretical framework for intervention in the trials. Death and weight gain are the two adverse events reported by the included trials. None of the trials reported health-related quality of life, morbidity, and costs as outcomes.

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Conclusion: TTM SOC and a combination of physical activity, diet and other interventions resulted in minimal weight loss, and there was no conclusive evidence for sustainable weight loss. The impact of TTM SOC as theoretical framework in weight loss management may depend on how it is used as a framework for intervention and in combination with other strategies like diet and physical activities.

Exercise Training for Adults with Chronic Kidney Disease

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Background: Chronic kidney disease (CKD) is a worldwide public health problem. In the National Kidney Foundation Disease Outcomes Quality Initiative Guidelines, it is stressed that lifestyle issues such as physical activity should be seen as cornerstones of the therapy. The physical fitness in adults with CKD is so reduced that it impinges on ability and capacity to perform activities in everyday life and occupational tasks. An increasing number of studies have been published regarding health effects of various regular exercise programs in adults with CKD and in renal transplant patients.

Objective: We aimed to: 1) assess the effects of regular exercise in adults with CKD and kidney transplant patients; and 2) determine how the exercise program should be designed (e.g. type, duration, intensity, frequency of exercise) to be able to affect physical fitness and functioning, level of physical activity, cardiovascular dimensions, nutrition, lipids, glucose metabolism, systemic inflammation, muscle morphology and morphometrics, dropout rates, compliance, adverse events and mortality.

Result: Forty-five studies, randomizing 1863 participants were included in this review. Thirty-two studies presented data that could be meta-analyzed. Types of exercise training included cardiovascular training, mixed cardiovascular and resistance training, resistance-only training and yoga. Some studies used supervised exercise interventions and others used unsupervised interventions. Exercise intensity was classed as 'high' or 'low', duration of individual exercise sessions ranged from 20 minutes/session to 110 minutes/session, and study duration was from two to 18 months. Seventeen percent of studies were classed as having an overall low risk of bias, 33% as moderate, and 49% as having a high risk of bias.

The results shows that regular exercise significantly improved: 1) physical fitness (aerobic capacity, 24 studies, 847 participants: SMD -0.56, 95% CI -0.70 to -0.42; walking capacity, 7 studies, 191 participants: SMD -0.36, 95% CI-0.65 to -0.06); 2) cardiovascular dimensions (resting diastolic blood pressure, 11 studies, 419 participants: MD 2.32 mm Hg, 95% CI 0.59 to 4.05; resting systolic blood pressure, 9 studies, 347 participants: MD 6.08 mm Hg, 95% CI 2.15 to 10.12; heart rate, 11 studies, 229 participants: MD 6 bpm, 95% CI 10 to 2); 3) some nutritional parameters (albumin, 3 studies, 111 participants: MD -2.28 g/L, 95% CI -4.25 to -0.32; pre-albumin, 3 studies, 111 participants: MD - 44.02 mg/L, 95% CI -71.52 to -16.53; energy intake, 4 studies, 97 participants: SMD -0.47, 95% CI -0.88 to -0.05); and 4) health-related quality of

life. Results also showed how exercise should be designed in order to optimize the effect. Other outcomes had insufficient evidence.

Conclusion: There is evidence for significant beneficial effects of regular exercise on physical fitness, walking capacity, cardiovascular dimensions (e.g. blood pressure and heart rate), health-related quality of life and some nutritional parameters in adults with CKD. Other outcomes had insufficient evidence due to the lack of data from RCTs. The design of the exercise intervention causes difference in effect size and should be considered when prescribing exercise with the aim of affecting a certain outcome. Future RCTs should focus more on the effects of resistance training interventions or mixed cardiovascular and resistance training as these types have not been studied as much as cardiovascular exercise.

Single Dose Oral Analgesics for Acute Postoperative Pain in Adults

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Background: Thirty-five Cochrane Reviews of randomized trials testing the analgesic efficacy of individual drug interventions in acute postoperative pain have been published. This overview brings together the results of all those reviews and assesses the reliability of available data.

Objective: To summarize data from all Cochrane Reviews that have assessed the effects of pharmaceutical interventions for acute pain in adults with at least moderate pain following surgery, who have been given a single dose of oral analgesic taken alone.

Result: The overview included 35 separate Cochrane Reviews with 38 analyses of single dose oral analgesics tested in acute postoperative pain models, with results from about 45,000 participants studied in approximately 350 individual studies. The individual reviews included only high-quality trials of standardized design and outcome reporting. The reviews used standardized methods and reporting for both efficacy and harm. Event rates with placebo were consistent in larger data sets. No statistical comparison was undertaken.

There were reviews but no trial data were available for Acemetacin, Meloxicam, Nabumetone, Nefopam, Sulindac, tenoxicam, and Tiaprofenic acid. Inadequate amounts of data were available for Dexibuprofen, Dextropropoxyphene 130 mg, diflunisal 125 mg, etoricoxib 60 mg, Fenbufen, and Indometacin. Where there was adequate information for drug/dose combinations (at least 200 participants, in at least two studies), we defined the addition of four comparisons of typical size (400 participants in total) with zero effect as making the result potentially subject to publication bias and therefore unreliable. Reliable results were obtained for 46 drug/dose combinations in all painful postsurgical conditions, 45 in dental pain and 14 in other painful conditions.

NNTs varied from about 1.5 to 20 for at least 50% maximum pain relief over four to six hours compared with placebo. The proportion of participants achieving this level of benefit varied from

about 30% to over 70%, and the time to re-medication varied from two hours (placebo) to over 20 hours in the same pain condition. Participants reporting at least one adverse event were few and generally no difference between active drug and placebo, with a few exceptions, principally for aspirin and opioids.

Drug/dose combinations with good (low) NNTs were ibuprofen 400 mg (2.5; 95% confidence interval (CI) 2.4 to 2.6), diclofenac 50 mg (2.7; 95% CI 2.4 to 3.0), etoricoxib 120 mg (1.9; 95% CI 1.7 to 2.1), codeine 60 mg + paracetamol 1000 mg (2.2; 95% CI 1.8 to 2.9), celecoxib 400 mg (2.5; 95% CI 2.2 to 2.9), and naproxen 500/550 mg (2.7; 95% CI 2.3 to 3.3). Long duration of action (≥ 8 hours) was found for etoricoxib 120 mg, diflunisal 500 mg, oxycodone 10 mg + paracetamol 650 mg, naproxen 500/550 mg, and celecoxib 400 mg.

Not all participants had good pain relief and for many drug/dose combinations 50% or more did not achieve at last 50% maximum pain relief over four to six hours.

Conclusion: There is a wealth of reliable evidence on the analgesic efficacy of single dose oral analgesics. There is also important information on drugs for which there are no data, inadequate data, or where results are unreliable due to susceptibility to publication bias.

Evening versus Morning Dosing Regimen Drug Therapy for Hypertension

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Background: Variation in blood pressure levels display circadian rhythms. The morning surge in blood pressure is known to increase the risk of myocardial events in the first several hours post awakening. A systematic review of the administration-time-related-effects of evening versus morning dosing regimen of antihypertensive drugs in the management of patients with primary hypertension has not been conducted.

Objective: To evaluate the administration-time-related-effects of antihypertensive drugs administered as once daily mono-therapy in the evening versus morning administration regimen on all cause mortality, cardiovascular morbidity and reduction of blood pressure in patients with primary hypertension.

Result: Twenty-one randomized controlled trials (RCTs) in 1,993 patients with primary hypertension met the inclusion criteria for this review - ACEIs (5 trials), CCBs (7 trials), ARBs (6 trials), diuretics (2 trials), alpha-blockers (1 trial), and beta-blockers (1 trial). Meta-analysis showed significant heterogeneity across trials.

No RCT reported on all cause mortality, cardiovascular mortality, cardiovascular morbidity and serious adverse events.

There was no statistically significant difference for overall adverse events (RR=0.78, 95%CI: 0.37 to 1.65) and withdrawals due to adverse events (RR=0.53, 95%CI: 0.26 to 1.07). No

significant differences were noted for morning SBP (-1.62 mm Hg, 95% CI: -4.19 to 0.95) and morning DBP (-1.21 mm Hg, 95% CI: -3.28 to 0.86); but 24-hour BP (SBP: -1.71 mm Hg, 95% CI: -2.78 to -0.65; DBP: -1.38 mm Hg, 95% CI: -2.13 to -0.62) showed a statistically significant difference.

Conclusion: No RCT reported on clinically relevant outcome measures - all cause mortality, cardiovascular morbidity and morbidity. There were no significant differences in overall adverse events and withdrawals due to adverse events among the evening versus morning dosing regimens. In terms of BP lowering efficacy, for 24-hour SBP and DBP, the data suggests that better blood pressure control was achieved with bedtime dosing than morning administration of antihypertensive medication, the clinical significance of which is not known.

Calcium Supplementation (Other than for Preventing or Treating Hypertension) for Improving Pregnancy and Infant Outcomes

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Background: Maternal nutrition during pregnancy is known to have an effect on fetal growth and development. It is recommended that women increase their calcium intake during pregnancy and lactation, although the recommended dosage varies among professionals. Currently, there is no consensus on the role of routine calcium supplementation for pregnant women other than for preventing or treating hypertension.

Objective: To determine the effect of calcium supplementation on maternal, fetal and neonatal outcomes (other than for preventing or treating hypertension) as well as any possible side effects.

Result: This review includes data from 21 studies (involving 16,602 women). There were no statistically significant differences between women who received calcium supplementation and those who did not in terms of reducing preterm births (less than 37 weeks' gestation) (risk ratio (RR) 0.90; 95% confidence interval (CI) 0.73 to 1.11; 12 studies, 15615 women; random-effects model) and also in less than 34 weeks' gestation (RR 1.11; 95% CI 0.84 to 1.46; three trials, 5145 women). There was no significant difference in infant low birth weight between the two groups (RR 0.91; 95% CI 0.72 to 1.16; four trials, 13449 infants; random-effects). However, compared to the control group, women in the calcium supplementation group gave birth to slightly heavier birth weight infants (mean difference (MD) 64.66 g; 95% CI 15.75 to 113.58; 19 trials, 8287 women; random-effects).

Conclusion: Calcium supplementation is associated with a significant protective benefit in the prevention of pre-eclampsia, and should be used for this indication according to a previous review. This review indicates that there are no additional benefits for calcium supplementation in prevention of preterm birth or low infant birth weight. While there was a statistically significant difference of 80g identified in mean infant birth weight, there was significant heterogeneity identified, and the clinical significance of this difference is uncertain.

Natalizumab for Relapsing Remitting Multiple Sclerosis

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Background: Natalizumab (NTZ) (Tysabri®) is a monoclonal antibody that inhibits leukocyte migration across the blood-brain barrier, thus reducing inflammation in central nervous system, and has been approved worldwide for the treatment of relapsing-remitting multiple sclerosis (RRMS).

Objective: To evaluate the efficacy, tolerability and safety of NTZ in the treatment of patients with RRMS.

Result: Three studies met the inclusion criteria. These included one placebo-controlled trial (942 patients) and two add-on placebo-controlled trials, i.e. one plus glatiramer acetate (110 patients) and the second plus interferon beta-1a (1171 patients).

This review assessed the efficacy, tolerability and safety of NTZ in patients with RRMS. Data was conclusive with respect to efficacy and tolerability, but not safety. As far as efficacy is concerned, the results showed statistically significant evidence in favor of NTZ for all the primary outcomes and for the secondary ones where data was available. NTZ reduced the risk of experiencing at least one new exacerbation at 2 years by about 40% and of experiencing progression at 2 years by about 25% as compared to a control group. MRI parameters showed statistical evidence in favor of participants receiving NTZ. Infusion reactions, anxiety, sinus congestion, lower limb swelling, rigors, vaginitis and menstrual disorders were reported as adverse events (AEs) more frequently after NTZ treatment. In this review, NTZ was found to be well tolerated over a follow-up period of two years: the number of patients experiencing at least one AE (including severe and serious AEs) during this period did not differ between NTZ-treated patients and controls. Safety concerns have been raised about Progressive Multifocal Leukoencephalopathy (PML). In the trials included in this review, two cases of PML were encountered: one in a patient who had received 29 doses of NTZ and a second fatal case of PML in another patient after 37 doses of NTZ. Our protocol was insufficient to evaluate PML risk as well as other rare and long-term adverse events such as cancers and other opportunistic infections, which are very important issues in considering the risk/benefit ratio of NTZ.

Conclusion: Although one trial did not contribute to efficacy results due to its duration, we found robust evidence in favor of a reduction in relapses and disability at 2 years in RRMS patients treated with NTZ. The drug was well tolerated. There are current significant safety concerns due to reporting of an increasing number of PML cases in patients treated with NTZ. This review was unable to provide an up-to-date systematic assessment of the risk due to the maximum 2 year-duration of the trials included. An independent systematic review of the safety profile of NTZ is warranted. NTZ should be used only by skilled neurologists in MS centers under surveillance programs.

All the data in this review came from trials supported by the Pharmaceutical Industry. In agreement with the Cochrane Collaboration policy, this may be considered a potential source of bias.