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BMJ (20 January 2017, Vol. 360, No. 8137)

Postsurgical prescriptions for opioid naive patients and association with overdose and misuse: Retrospective cohort study
Gabriel A Brat, Denis Agniel, Andrew Beam, et al.
BMJ 2018; 360 (Published 17 January 2018)
http://www.bmj.com/content/360/bmj.j5790

Abstract
Objective To quantify the effects of varying opioid prescribing patterns after surgery on dependence, overdose, or abuse in an opioid naive population.
Design Retrospective cohort study.
Setting Surgical claims from a linked medical and pharmacy administrative database of 37 651 619 commercially insured patients between 2008 and 2016.
Participants 1 015 116 opioid naive patients undergoing surgery.
Main outcome measures Use of oral opioids after discharge as defined by refills and total dosage and duration of use. The primary outcome was a composite of misuse identified by a diagnostic code for opioid dependence, abuse, or overdose.
Results 568 612 (56.0%) patients received postoperative opioids, and a code for abuse was identified for 5906 patients (0.6%, 183 per 100 000 person years). Total duration of opioid use was the strongest predictor of misuse, with each refill and additional week of opioid use associated with an adjusted increase in the rate of misuse of 44.0% (95% confidence interval 40.8% to 47.2%, P<0.001), and 19.9% increase in hazard (18.5% to 21.4%, P<0.001), respectively.
Conclusions Each refill and week of opioid prescription is associated with a large increase in opioid misuse among opioid naive patients. The data from this study suggest that duration of the prescription rather than dosage is more strongly associated with

ultimate misuse in the early postsurgical period. The analysis quantifies the association of prescribing choices on opioid misuse and identifies levers for possible impact.

Development and validation of outcome prediction models for aneurysmal subarachnoid haemorrhage: The SAHIT multinational cohort study

Blessing N R Jaja, Gustavo Saposnik, Hester F Lingsma, et al. on behalf of the SAHIT collaboration

BMJ 2018; 360 (Published 18 January 2018)
http://www.bmj.com/content/360/bmj.j5745

Abstract

Objective To develop and validate a set of practical prediction tools that reliably estimate the outcome of subarachnoid haemorrhage from ruptured intracranial aneurysms (SAH).

Design Cohort study with logistic regression analysis to combine predictors and treatment modality.

Setting Subarachnoid Haemorrhage International Trialists' (SAHIT) data repository, including randomised clinical trials, prospective observational studies, and hospital registries.

Participants Researchers collaborated to pool datasets of prospective observational studies, hospital registries, and randomised clinical trials of SAH from multiple geographical regions to develop and validate clinical prediction models.

Main outcome measure Predicted risk of mortality or functional outcome at three months according to score on the Glasgow outcome scale.

Results Clinical prediction models were developed with individual patient data from 10 936 patients and validated with data from 3355 patients after development of the model. In the validation cohort, a core model including patient age, premorbid hypertension, and neurological grade on admission to predict risk of functional outcome had good discrimination, with an area under the receiver operator characteristics curve (AUC) of 0.80 (95% confidence interval 0.78 to 0.82). When the core model was extended to a "neuroimaging model," with inclusion of clot volume, aneurysm size, and location, the AUC improved to 0.81 (0.79 to 0.84). A full model that extended the neuroimaging model by including treatment modality had AUC of 0.81 (0.79 to 0.83). Discrimination was lower for a similar set of models to predict risk of mortality (AUC for full model 0.76, 0.69 to 0.82). All models showed satisfactory calibration in the validation cohort.

Conclusion The prediction models reliably estimate the outcome of patients who were managed in various settings for ruptured intracranial aneurysms that caused subarachnoid haemorrhage. The predictor items are readily derived at hospital admission. The web based SAHIT prognostic calculator (http://sahitscore.com) and the related app could be adjunctive tools to support management of patients.

Concerns about composite reference standards in diagnostic research

Nandini Dendukuri, Ian Schiller, Joris de Groot, et al.

BMJ 2018; 360 (Published 18 January 2018)
http://www.bmj.com/content/360/bmj.j5779

Summary points

- Composite reference standards define a fixed, transparent rule to classify subjects into disease positive and disease negative groups based on existing imperfect tests

- They are widely regarded as appropriate for determining sensitivity and specificity of a new test in the absence of a perfect reference test
- Though a composite reference standard is attractive for its simple and transparent construction, it can result in biased estimates as it makes suboptimal use of data
- Bias due to a composite reference standard can worsen as more information is gathered and the new test's accuracy can be overestimated if the errors made by the composite reference standard and the new test are correlated
- Composite reference standards cannot aid standardisation across settings when disease prevalence varies
- Appropriately constructed latent class models should be used to make complete use of the information gathered from multiple imperfect tests

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JAMA: Journal of the American Medical Association (23-30 January 2018, Vol. 319, No. 4)

Effect of Prolonged Exposure Therapy Delivered Over 2 Weeks vs 8 Weeks vs Present-Centered Therapy on PTSD Symptom Severity in Military Personnel: A Randomized Clinical Trial

Edna B. Foa, Carmen P. McLean, Yinyin Zang, et al for the STRONG STAR Consortium

JAMA. 2018; 319 (4): 354-364.
https://jamanetwork.com/journals/jama/fullarticle/2670254

Abstract

Importance Effective and efficient treatment is needed for posttraumatic stress disorder (PTSD) in active duty military personnel.

Objective To examine the effects of massed prolonged exposure therapy (massed therapy), spaced prolonged exposure therapy (spaced therapy), present-centered therapy (PCT), and a minimal-contact control (MCC) on PTSD severity.

Design, Setting, and Participants Randomized clinical trial conducted at Fort Hood, Texas, from January 2011 through July 2016 and enrolling 370 military personnel with PTSD who had returned from Iraq, Afghanistan, or both. Final follow-up was July 11, 2016.

Interventions Prolonged exposure therapy, cognitive behavioral therapy involving exposure to trauma memories/reminders, administered as massed therapy (n = 110; 10 sessions over 2 weeks) or spaced therapy (n = 109; 10 sessions over 8 weeks); PCT, a non–trauma-focused therapy involving identifying/discussing daily stressors (n = 107; 10 sessions over 8 weeks); or MCC, telephone calls from therapists (n = 40; once weekly for 4 weeks.(

Main Outcomes and Measure Outcomes were assessed before and after treatment and at 2-week, 12-week, and 6-month follow-up. Primary outcome was interviewer-assessed PTSD symptom severity, measured by the PTSD Symptom Scale–Interview (PSS-I; range, 0-51; higher scores indicate greater PTSD severity; MCID, 3.18), used to assess efficacy of massed therapy at 2 weeks posttreatment vs MCC at week 4; noninferiority of massed therapy vs spaced therapy at 2 weeks and 12 weeks posttreatment (noninferiority margin, 50% [2.3 points on PSS-I, with 1-sided α = .05 **;**([and efficacy of spaced therapy vs PCT at posttreatment.

Results Among 370 randomized participants, data were analyzed for 366 (mean age, 32.7 [SD, 7.3] years; 44 women [12.0%]; mean baseline PSS-I score, 25.49 [6.36]), and 216 (59.0%) completed the study. At 2 weeks posttreatment, mean PSS-I score was 17.62 (mean decrease from baseline, 7.13) for massed therapy and 21.41 (mean decrease,

3.43) for MCC (difference in decrease, 3.70 [95% CI,0.72 to 6.68 ;[*P* .(02. = At 2 weeks posttreatment, mean PSS-I score was 18.03 for spaced therapy (decrease, 7.29; difference in means vs massed therapy, 0.79 [1-sided 95% CI, −∞ to 2.29 ;*P* 049. =for noninferiority]) and at 12 weeks posttreatment was 18.88 for massed therapy (decrease, 6.32) and 18.34 for spaced therapy (decrease, 6.97; difference, 0.55 [1-sided 95% CI, −∞ to 2.05 ;*P* 03. =for noninferiority]). At posttreatment, PSS-I scores for PCT were 18.65 (decrease, 7.31; difference in decrease vs spaced therapy, 0.10 [95% CI, −2.48 to 2.27 ;[*P*.(93. =

Conclusions and Relevance Among active duty military personnel with PTSD, massed therapy (10 sessions over 2 weeks) reduced PTSD symptom severity more than MCC at 2-week follow-up and was noninferior to spaced therapy (10 sessions over 8 weeks), and there was no significant difference between spaced therapy and PCT. The reductions in PTSD symptom severity with all treatments were relatively modest, suggesting that further research is needed to determine the clinical importance of these findings.

Association Between Left Atrial Appendage Occlusion and Readmission for Thromboembolism Among Patients With Atrial Fibrillation Undergoing Concomitant Cardiac Surgery

Daniel J. Friedman, Jonathan P. Piccini, Tongrong Wang, et al.

JAMA. 2018; 319 (4): 365-374.
https://jamanetwork.com/journals/jama/article-abstract/2670253?redirect=true

Abstract

Importance The left atrial appendage is a key site of thrombus formation in atrial fibrillation (AF) and can be occluded or removed at the time of cardiac surgery. There is limited evidence regarding the effectiveness of surgical left atrial appendage occlusion (S-LAAO) for reducing the risk of thromboembolism.

Objective To evaluate the association of S-LAAO vs no receipt of S-LAAO with the risk of thromboembolism among older patients undergoing cardiac surgery.

Design, Setting, and Participants Retrospective cohort study of a nationally representative Medicare-linked cohort from the Society of Thoracic Surgeons Adult Cardiac Surgery Database (2011-2012). Patients aged 65 years and older with AF undergoing cardiac surgery (coronary artery bypass grafting [CABG], mitral valve surgery with or without CABG, or aortic valve surgery with or without CABG) with and without concomitant S-LAAO were followed up until December 31, 2014.

Exposures S-LAAO vs no S-LAAO.

Main Outcomes and Measures The primary outcome was readmission for thromboembolism (stroke, transient ischemic attack, or systemic embolism) at up to 3 years of follow-up, as defined by Medicare claims data. Secondary end points included hemorrhagic stroke, all-cause mortality, and a composite end point (thromboembolism, hemorrhagic stroke, or all-cause mortality).

Results Among 10 524 patients undergoing surgery (median age, 76 years; 39% female; median CHA_2DS_2-VASc score, 4), 3892 (37%) underwent S-LAAO. Overall, at a mean follow-up of 2.6 years, thromboembolism occurred in 5.4%, hemorrhagic stroke in 0.9%, all-cause mortality in 21.5%, and the composite end point in 25.7%. S-LAAO, compared with no S-LAAO, was associated with lower unadjusted rates of thromboembolism (4.2% vs 6.2%), all-cause mortality (17.3% vs 23.9%), and the composite end point (20.5% vs 28.7%) but no significant difference in rates of hemorrhagic stroke (0.9% vs 0.9%). After inverse probability–weighted adjustment, S-LAAO was associated with a significantly lower rate of thromboembolism (subdistribution hazard ratio [HR], 0.67; 95% CI, 0.56-0.81;

P < .001), all-cause mortality (HR, 0.88; 95% CI, 0.79-0.97; *P* = .001), and the composite end point (HR, 0.83; 95% CI, 0.76-0.91; *P* < .001) but not hemorrhagic stroke (subdistribution HR, 0.84; 95% CI, 0.53-1.32; *P* = .44). S-LAAO, compared with no S-LAAO, was associated with a lower risk of thromboembolism among patients discharged without anticoagulation (unadjusted rate, 4.2% vs 6.0%; adjusted subdistribution HR, 0.26; 95% CI, 0.17-0.40; *P* < .001), but not among patients discharged with anticoagulation (unadjusted rate, 4.1% vs 6.3%; adjusted subdistribution HR, 0.88; 95% CI, 0.56-1.39; *P* = .59).

Conclusions and Relevance Among older patients with AF undergoing concomitant cardiac surgery, S-LAAO, compared with no S-LAAO, was associated with a lower risk of readmission for thromboembolism over 3 years. These findings support the use of S-LAAO, but randomized trials are necessary to provide definitive evidence.

Association of Hysteroscopic vs Laparoscopic Sterilization With Procedural, Gynecological, and Medical Outcomes

Kim Bouillon, Marion Bertrand, Georges Bader, et al.

JAMA. 2018; 319 (4): 375-387.

https://jamanetwork.com/journals/jama/article-abstract/2670255?redirect=true

Abstract

Importance Safety of hysteroscopic sterilization has been recently questioned following reports of general symptoms such as allergy, tiredness, and depression in addition to associated gynecological results such as pelvic pain, perforation of fallopian tubes or uterus, and unwanted pregnancy.

Objective To compare the risk of reported adverse events between hysteroscopic and laparoscopic sterilization.

Design, Setting, and Participants French nationwide cohort study using the national hospital discharge database linked to the health insurance claims database. Women aged 30 to 54 years receiving a first hysteroscopic or laparoscopic sterilization between 2010 and 2014 were included and were followed up through December 2015.

Exposures Hysteroscopic sterilization vs laparoscopic sterilization.

Main Outcomes and Measures Risks of procedural complications (surgical and medical) and of gynecological (sterilization failure that includes salpingectomy, second sterilization procedure, or pregnancy; pregnancy; reoperation) and medical outcomes (all types of allergy; autoimmune diseases; thyroid disorder; use of analgesics, antimigraines, antidepressants, benzodiazepines; outpatient visits; sickness absence; suicide attempts; death) that occurred within 1 and 3 years after sterilization were compared using inverse probability of treatment–weighted Cox models.

Results Of the 105 357 women included (95.5% of eligible participants; mean age, 41.3 years [SD, 3.7 years]), 71 303 (67.7%) underwent hysteroscopic sterilization, and 34 054 (32.3%) underwent laparoscopic sterilization. During the hospitalization for sterilization, risk of surgical complications for hysteroscopic sterilization was lower: 0.13% for hysteroscopic sterilization vs 0.78% for laparoscopic sterilization (adjusted risk difference [RD], −0.64; 95% CI, −0.67 to −0.60) and was lower for medical complications: 0.06% vs 0.11% (adjusted RD, −0.05; 95% CI, −0.08 to −0.01). During the first year after sterilization, 4.83% of women who underwent hysteroscopic sterilization had a higher risk of sterilization failure than the 0.69% who underwent laparoscopic sterilization (adjusted hazard ratio [HR], 7.11; 95% CI, 5.92 to 8.54; adjusted RD, 4.23 per 100 person-years; 95% CI, 3.40 to 5.22). Additionally, 5.65% of women who underwent hysteroscopic sterilization required gynecological reoperation vs 1.76% of women who underwent

laparoscopic sterilization (adjusted HR, 3.26; 95% CI, 2.90 to 3.67; adjusted RD, 4.63 per 100 person-years; 95% CI, 3.38 to 4.75); these differences persisted after 3 years, although attenuated. Hysteroscopic sterilization was associated with a lower risk of pregnancy within the first year of the procedure but was not significantly associated with a difference in risk of pregnancy by the third year (adjusted HR, 1.04; 95% CI, 0.83-1.30; adjusted RD, 0.01 per 100 person-years; 95% CI, −0.04 to 0.07). Risks of medical outcomes were not significantly increased with hysteroscopic sterilization compared with laparoscopic sterilization.

Conclusions and Relevance Among women undergoing first sterilization, the use of hysteroscopic sterilization was significantly associated with higher risk of gynecological complications over 1 year and over 3 years than was laparoscopic sterilization. Risk of medical outcomes was not significantly increased over 1 year or over 3 years. These findings do not support increased medical risks associated with hysteroscopic sterilization.

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The Lancet (20 January 2018, Vol. 391, No. 10117)

Rivaroxaban with or without aspirin in patients with stable coronary artery disease: An international, randomised, double-blind, placebo-controlled trial

Stuart J Connolly, John W Eikelboom, Jackie Bosch et al. on behalf of the show COMPASS investigators

The Lancet: Volume 391, No. 10117, p205–218, 20 January 2018
http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(17)32458-3/fulltext

Summary

Background

Coronary artery disease is a major cause of morbidity and mortality worldwide, and is a consequence of acute thrombotic events involving activation of platelets and coagulation proteins. Factor Xa inhibitors and aspirin each reduce thrombotic events but have not yet been tested in combination or against each other in patients with stable coronary artery disease.

Methods

In this multicentre, double-blind, randomised, placebo-controlled, outpatient trial, patients with stable coronary artery disease or peripheral artery disease were recruited at 602 hospitals, clinics, or community centres in 33 countries. This paper reports on patients with coronary artery disease. Eligible patients with coronary artery disease had to have had a myocardial infarction in the past 20 years, multi-vessel coronary artery disease, history of stable or unstable angina, previous multi-vessel percutaneous coronary intervention, or previous multi-vessel coronary artery bypass graft surgery. After a 30-day run in period, patients were randomly assigned (1:1:1) to receive rivaroxaban (2·5 mg orally twice a day) plus aspirin (100 mg once a day), rivaroxaban alone (5 mg orally twice a day), or aspirin alone (100 mg orally once a day). Randomisation was computer generated. Each treatment group was double dummy, and the patients, investigators, and central study staff were masked to treatment allocation. The primary outcome of the COMPASS trial was the occurrence of myocardial infarction, stroke, or cardiovascular death. This trial is registered with ClinicalTrials.gov, number NCT01776424, and is closed to new participants.

Findings

Between March 12, 2013, and May 10, 2016, 27 395 patients were enrolled to the COMPASS trial, of whom 24 824 patients had stable coronary artery disease from 558

centres. The combination of rivaroxaban plus aspirin reduced the primary outcome more than aspirin alone (347 [4%] of 8313 *vs* 460 [6%] of 8261; hazard ratio [HR] 0·74, 95% CI 0·65–0·86, p<0·0001). By comparison, treatment with rivaroxaban alone did not significantly improve the primary outcome when compared with treatment with aspirin alone (411 [5%] of 8250 *vs* 460 [6%] of 8261; HR 0·89, 95% CI 0·78–1·02, p=0·094). Combined rivaroxaban plus aspirin treatment resulted in more major bleeds than treatment with aspirin alone (263 [3%] of 8313 *vs* 158 [2%] of 8261; HR 1·66, 95% CI 1·37–2·03, p<0·0001), and similarly, more bleeds were seen in the rivaroxaban alone group than in the aspirin alone group (236 [3%] of 8250 *vs* 158 [2%] of 8261; HR 1·51, 95% CI 1·23–1·84, p<0·0001). The most common site of major bleeding was gastrointestinal, occurring in 130 [2%] patients who received combined rivaroxaban plus aspirin, in 84 [1%] patients who received rivaroxaban alone, and in 61 [1%] patients who received aspirin alone. Rivaroxaban plus aspirin reduced mortality when compared with aspirin alone (262 [3%] of 8313 *vs* 339 [4%] of 8261; HR 0·77, 95% CI 0·65–0·90, p=0·0012).

Interpretation

In patients with stable coronary artery disease, addition of rivaroxaban to aspirin lowered major vascular events, but increased major bleeding. There was no significant increase in intracranial bleeding or other critical organ bleeding. There was also a significant net benefit in favour of rivaroxaban plus aspirin and deaths were reduced by 23%. Thus, addition of rivaroxaban to aspirin has the potential to substantially reduce morbidity and mortality from coronary artery disease worldwide.

Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: An international, randomised, double-blind, placebo-controlled trial

Sonia S Anand, Jackie Bosch, John W Eikelboom, et al. on behalf of the show COMPASS Investigators

The Lancet: Volume 391, No. 10117, p219–229, 20 January 2018
http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(17)32409-1/fulltext

Summary

Background

Patients with peripheral artery disease have an increased risk of cardiovascular morbidity and mortality. Antiplatelet agents are widely used to reduce these complications.

Methods

This was a multicentre, double-blind, randomised placebo-controlled trial for which patients were recruited at 602 hospitals, clinics, or community practices from 33 countries across six continents. Eligible patients had a history of peripheral artery disease of the lower extremities (previous peripheral bypass surgery or angioplasty, limb or foot amputation, intermittent claudication with objective evidence of peripheral artery disease), of the carotid arteries (previous carotid artery revascularisation or asymptomatic carotid artery stenosis of at least 50%), or coronary artery disease with an ankle–brachial index of less than 0·90. After a 30-day run-in period, patients were randomly assigned (1:1:1) to receive oral rivaroxaban (2·5 mg twice a day) plus aspirin (100 mg once a day), rivaroxaban twice a day (5 mg with aspirin placebo once a day), or to aspirin once a day (100 mg and rivaroxaban placebo twice a day). Randomisation was computer generated. Each treatment group was double dummy, and the patient, investigators, and central study staff were masked to treatment allocation. The primary outcome was cardiovascular death, myocardial infarction or stroke; the primary peripheral artery disease outcome was major adverse limb events including major amputation. This trial is registered with ClinicalTrials.gov, number NCT01776424, and is closed to new participants.

Findings
Between March 12, 2013, and May 10, 2016, we enrolled 7470 patients with peripheral artery disease from 558 centres. The combination of rivaroxaban plus aspirin compared with aspirin alone reduced the composite endpoint of cardiovascular death, myocardial infarction, or stroke (126 [5%] of 2492 *vs* 174 [7%] of 2504; hazard ratio [HR] 0·72, 95% CI 0·57–0·90, p=0·0047), and major adverse limb events including major amputation (32 [1%] *vs* 60 [2%]; HR 0·54 95% CI 0·35–0·82, p=0·0037). Rivaroxaban 5 mg twice a day compared with aspirin alone did not significantly reduce the composite endpoint (149 [6%] of 2474 *vs* 174 [7%] of 2504; HR 0·86, 95% CI 0·69–1·08, p=0·19), but reduced major adverse limb events including major amputation (40 [2%] *vs* 60 [2%]; HR 0·67, 95% CI 0·45–1·00, p=0·05). The median duration of treatment was 21 months. The use of the rivaroxaban plus aspirin combination increased major bleeding compared with the aspirin alone group (77 [3%] of 2492 *vs* 48 [2%] of 2504; HR 1·61, 95% CI 1·12–2·31, p=0·0089), which was mainly gastrointestinal. Similarly, major bleeding occurred in 79 (3%) of 2474 patients with rivaroxaban 5 mg, and in 48 (2%) of 2504 in the aspirin alone group (HR 1·68, 95% CI 1·17–2·40; p=0·0043).
Interpretation
Low-dose rivaroxaban taken twice a day plus aspirin once a day reduced major adverse cardiovascular and limb events when compared with aspirin alone. Although major bleeding was increased, fatal or critical organ bleeding was not. This combination therapy represents an important advance in the management of patients with peripheral artery disease. Rivaroxaban alone did not significantly reduce major adverse cardiovascular events compared with asprin alone, but reduced major adverse limb events and increased major bleeding.

Effects of teriparatide and risedronate on new fractures in post-menopausal women with severe osteoporosis (VERO): A multicentre, double-blind, double-dummy, randomised controlled trial
David L Kendler, Fernando Marin, Cristiano A F Zerbini, et al.
The Lancet: Volume 391, No. 10117, p230–240, 20 January 2018
http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(17)32137-2/fulltext

Summary
Background
No clinical trials have compared osteoporosis drugs with incident fractures as the primary outcome. We compared the anti-fracture efficacy of teriparatide with risedronate in patients with severe osteoporosis.
Methods
In this double-blind, double-dummy trial, we enrolled post-menopausal women with at least two moderate or one severe vertebral fracture and a bone mineral density T score of less than or equal to −1·50. Participants were randomly assigned to receive 20 μg of teriparatide once daily plus oral weekly placebo or 35 mg of oral risedronate once weekly plus daily injections of placebo for 24 months. The primary outcome was new radiographic vertebral fractures. Secondary, gated outcomes included new and worsened radiographic vertebral fractures, clinical fractures (a composite of non-vertebral and symptomatic vertebral), and non-vertebral fractures. This study is registered with ClinicalTrials.gov (NCT01709110) and EudraCT (2012-000123-41).
Findings
We enrolled 680 patients in each group. At 24 months, new vertebral fractures occurred in 28 (5·4%) of 680 patients in the teriparatide group and 64 (12·0%) of 680 patients in the

risedronate group (risk ratio 0·44, 95% CI 0·29–0·68; p<0·0001). Clinical fractures occurred in 30 (4·8%) of 680 patients in the teriparatide group compared with 61 (9·8%) of 680 in the risedronate group (hazard ratio 0·48, 95% CI 0·32–0·74; p=0·0009). Non-vertebral fragility fractures occurred in 25 (4·0%) patients in the teriparatide group and 38 (6·1%) in the risedronate group (hazard ratio 0·66; 95% CI 0·39–1·10; p=0·10).

Interpretation

Among post-menopausal women with severe osteoporosis, the risk of new vertebral and clinical fractures is significantly lower in patients receiving teriparatide than in those receiving risedronate.

Morbidity and mortality in homeless individuals, prisoners, sex workers, and individuals with substance use disorders in high-income countries: A systematic review and meta-analysis

Robert W Aldridge, Alistair Story, Stephen W Hwang, et al.

The Lancet: Volume 391, No. 10117, p241–250, 20 January 2018
http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(17)31869-X/fulltext

Summary

Background

Inclusion health focuses on people in extremely poor health due to poverty, marginalisation, and multimorbidity. We aimed to review morbidity and mortality data on four overlapping populations who experience considerable social exclusion: homeless populations, individuals with substance use disorders, sex workers, and imprisoned individuals.

Methods

For this systematic review and meta-analysis, we searched MEDLINE, Embase, and the Cochrane Library for studies published between Jan 1, 2005, and Oct 1, 2015. We included only systematic reviews, meta-analyses, interventional studies, and observational studies that had morbidity and mortality outcomes, were published in English, from high-income countries, and were done in populations with a history of homelessness, imprisonment, sex work, or substance use disorder (excluding cannabis and alcohol use). Studies with only perinatal outcomes and studies of individuals with a specific health condition or those recruited from intensive care or high dependency hospital units were excluded. We screened studies using systematic review software and extracted data from published reports. Primary outcomes were measures of morbidity (prevalence or incidence) and mortality (standardised mortality ratios [SMRs] and mortality rates). Summary estimates were calculated using a random effects model.

Findings

Our search identified 7946 articles, of which 337 studies were included for analysis. All-cause standardised mortality ratios were significantly increased in 91 (99%) of 92 extracted datapoints and were 11·86 (95% CI 10·42–13·30; I^2=94·1%) in female individuals and 7·88 (7·03–8·74; I^2=99·1%) in men. Summary SMR estimates for the International Classification of Diseases disease categories with two or more included datapoints were highest for deaths due to injury, poisoning, and other external causes, in both men (7·89; 95% CI 6·40–9·37; I^2=98·1%) and women (18·72; 13·73–23·71; I^2=91·5%). Disease prevalence was consistently raised across the following categories: infections (eg, highest reported was 90% for hepatitis C, 67 [65%] of 103 individuals for hepatitis B, and 133 [51%] of 263 individuals for latent tuberculosis infection), mental health (eg, highest reported was 9 [4%] of 227 individuals for schizophrenia), cardiovascular conditions (eg, highest reported was 32 [13%] of 247 individuals for

coronary heart disease), and respiratory conditions (e.g. highest reported was 9 [26%] of 35 individuals for asthma).

Interpretation

Our study shows that homeless populations, individuals with substance use disorders, sex workers, and imprisoned individuals experience extreme health inequities across a wide range of health conditions, with the relative effect of exclusion being greater in female individuals than male individuals. The high heterogeneity between studies should be explored further using improved data collection in population subgroups. The extreme health inequity identified demands intensive cross-sectoral policy and service action to prevent exclusion and improve health outcomes in individuals who are already marginalised.

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The New England Journal of Medicine (18 January 2018, Vol. 378, No. 3)

Household-Contact Investigation for Detection of Tuberculosis in Vietnam

Greg J. Fox, Nguyen V. Nhung, Dinh N. Sy, et al.

N Engl J Med 2018; 378: 221-229 January 18, 2018
http://www.nejm.org/doi/full/10.1056/NEJMoa1700209

Abstract

Background

Active case finding is a top priority for the global control of tuberculosis, but robust evidence for its effectiveness in high-prevalence settings is lacking. We sought to evaluate the effectiveness of household-contact investigation, as compared with standard, passive measures alone, in Vietnam.

Methods

We performed a cluster-randomized, controlled trial at clinics in 70 districts (local government areas with an average population of approximately 500,000 in urban areas and 100,000 in rural areas) in eight provinces of Vietnam. Health workers at each district clinic or hospital were assigned to perform either household-contact intervention plus standard passive case finding (intervention group) or passive case finding alone (control group). In the intervention districts, household contacts of patients with positive results for tuberculosis on sputum smear microscopy (smear-positive tuberculosis) were invited for clinical assessment and chest radiography at baseline and at 6, 12, and 24 months. The primary outcome was the cumulative incidence of registered cases of tuberculosis among household contacts of patients with tuberculosis during a 2-year period.

Results

In 70 selected districts, we enrolled 25,707 household contacts of 10,964 patients who had smear-positive pulmonary tuberculosis. In the 36 districts that were included in the intervention group, 180 of 10,069 contacts were registered as having tuberculosis (1788 cases per 100,000 population), as compared with 110 of 15,638 contacts (703 per 100,000) in the control group (relative risk of the primary outcome in the intervention group, 2.5; 95% confidence interval [CI], 2.0 to 3.2; P<0.001); the relative risk of smear-positive disease among household contacts in the intervention group was 6.4 (95% CI, 4.5 to 9.0; P<0.001).

Conclusions

Household-contact investigation plus standard passive case finding was more effective than standard passive case finding alone for the detection of tuberculosis in a high-prevalence setting at 2 years.

Hyperthermic Intraperitoneal Chemotherapy in Ovarian Cancer
Willemien J. van Driel, Simone N. Koole, Karolina Sikorska, et al.
N Engl J Med 2018; 378: 230-240 January 18, 2018
http://www.nejm.org/doi/full/10.1056/NEJMoa1708618

Abstract

Background

Treatment of newly diagnosed advanced-stage ovarian cancer typically involves cytoreductive surgery and systemic chemotherapy. We conducted a trial to investigate whether the addition of hyperthermic intraperitoneal chemotherapy (HIPEC) to interval cytoreductive surgery would improve outcomes among patients who were receiving neoadjuvant chemotherapy for stage III epithelial ovarian cancer.

Methods

In a multicenter, open-label, phase 3 trial, we randomly assigned 245 patients who had at least stable disease after three cycles of carboplatin (area under the curve of 5 to 6 mg per milliliter per minute) and paclitaxel (175 mg per square meter of body-surface area) to undergo interval cytoreductive surgery either with or without administration of HIPEC with cisplatin (100 mg per square meter). Randomization was performed at the time of surgery in cases in which surgery that would result in no visible disease (complete cytoreduction) or surgery after which one or more residual tumors measuring 10 mm or less in diameter remain (optimal cytoreduction) was deemed to be feasible. Three additional cycles of carboplatin and paclitaxel were administered postoperatively. The primary end point was recurrence-free survival. Overall survival and the side-effect profile were key secondary end points.

Results

In the intention-to-treat analysis, events of disease recurrence or death occurred in 110 of the 123 patients (89%) who underwent cytoreductive surgery without HIPEC (surgery group) and in 99 of the 122 patients (81%) who underwent cytoreductive surgery with HIPEC (surgery-plus-HIPEC group) (hazard ratio for disease recurrence or death, 0.66; 95% confidence interval [CI], 0.50 to 0.87; P=0.003). The median recurrence-free survival was 10.7 months in the surgery group and 14.2 months in the surgery-plus-HIPEC group. At a median follow-up of 4.7 years, 76 patients (62%) in the surgery group and 61 patients (50%) in the surgery-plus-HIPEC group had died (hazard ratio, 0.67; 95% CI, 0.48 to 0.94; P=0.02). The median overall survival was 33.9 months in the surgery group and 45.7 months in the surgery-plus-HIPEC group. The percentage of patients who had adverse events of grade 3 or 4 was similar in the two groups (25% in the surgery group and 27% in the surgery-plus-HIPEC group, P=0.76).

Conclusions

Among patients with stage III epithelial ovarian cancer, the addition of HIPEC to interval cytoreductive surgery resulted in longer recurrence-free survival and overall survival than surgery alone and did not result in higher rates of side effects.

Long-Term Follow-up of Monoclonal Gammopathy of Undetermined Significance
Robert A. Kyle, Dirk R. Larson, Terry M. Therneau, et al.
N Engl J Med 2018; 378: 241-249 January 18, 2018
http://www.nejm.org/doi/full/10.1056/NEJMoa1709974

Abstract
Background
Monoclonal gammopathy of undetermined significance (MGUS) occurs in approximately 3% of persons 50 years of age or older.
Methods
We studied 1384 patients who were residing in southeastern Minnesota and in whom MGUS was diagnosed at the Mayo Clinic in the period from 1960 through 1994; the median follow-up was 34.1 years (range, 0.0 to 43.6). The primary end point was progression to multiple myeloma or another plasma-cell or lymphoid disorder.
Results
During 14,130 person-years of follow-up, MGUS progressed in 147 patients (11%), a rate that was 6.5 times (95% confidence interval [CI], 5.5 to 7.7) as high as the rate in the control population. The risk of progression without accounting for death due to competing causes was 10% at 10 years, 18% at 20 years, 28% at 30 years, 36% at 35 years, and 36% at 40 years. Among patients with IgM MGUS, the presence of two adverse risk factors — namely, an abnormal serum free light-chain ratio (ratio of kappa to lambda free light chains) and a high serum monoclonal protein (M protein) level (≥1.5 g per deciliter) — was associated with a risk of progression at 20 years of 55%, as compared with 41% among patients who had one adverse risk factor and 19% among patients who had neither risk factor. Among patients with non-IgM MGUS, the risk of progression at 20 years was 30% among those who had the two risk factors, 20% among those who had one risk factor, and 7% among those who had neither risk factor. Patients with MGUS had shorter survival than was expected in the control population of Minnesota residents of matched age and sex (median, 8.1 vs. 12.4 years; P<0.001).
Conclusions
Significant differences were noted in the risk of progression between patients with IgM MGUS and those with non-IgM MGUS. Overall survival was shorter among patients with MGUS than was expected in a matched control population.

Somatic Activating KRAS Mutations in Arteriovenous Malformations of the Brain
Sergey I. Nikolaev, Sandra Vetiska, Ximena Bonilla, et al.
N Engl J Med 2018; 378:250-261 January 18, 2018
http://www.nejm.org/doi/full/10.1056/NEJMoa1709449

Abstract
Background
Sporadic arteriovenous malformations of the brain, which are morphologically abnormal connections between arteries and veins in the brain vasculature, are a leading cause of hemorrhagic stroke in young adults and children. The genetic cause of this rare focal disorder is unknown.
Methods
We analyzed tissue and blood samples from patients with arteriovenous malformations of the brain to detect somatic mutations. We performed exome DNA sequencing of tissue samples of arteriovenous malformations of the brain from 26 patients in the main study group and of paired blood samples from 17 of those patients. To confirm our findings, we performed droplet digital polymerase-chain-reaction (PCR) analysis of tissue samples from 39 patients in the main study group (21 with matching blood samples) and from 33 patients in an independent validation group. We interrogated the downstream signaling pathways, changes in gene expression, and cellular phenotype that were induced by activating KRAS mutations, which we had discovered in tissue samples.

Results
We detected somatic activating KRAS mutations in tissue samples from 45 of the 72 patients and in none of the 21 paired blood samples. In endothelial cell–enriched cultures derived from arteriovenous malformations of the brain, we detected KRAS mutations and observed that expression of mutant KRAS (KRASG12V) in endothelial cells in vitro induced increased ERK (extracellular signal-regulated kinase) activity, increased expression of genes related to angiogenesis and Notch signaling, and enhanced migratory behavior. These processes were reversed by inhibition of MAPK (mitogen-activated protein kinase)–ERK signaling.
Conclusions
We identified activating KRAS mutations in the majority of tissue samples of arteriovenous malformations of the brain that we analyzed. We propose that these malformations develop as a result of KRAS-induced activation of the MAPK–ERK signaling pathway in brain endothelial cells.

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Sources

BMJ: British Medical Journal	http://www.bmj.com/theBMJ
JAMA: The Journal of the American Medical Association	http://jama.ama-assn.org/
The Lancet	www.thelancet.com
The New England Journal of Medicine	http://content.nejm.org/
The British Medical Journal (BMJ), JAMA and the New England Journal of Medicine (NEJM) can be accessed in full-text through your NHS Athens account. Unfortunately the national subscription to The Lancet has been cancelled.	https://www.evidence.nhs.uk/nhs-evidence-content/journals-and-databases or http://www.openathens.net/
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ClinicalKey

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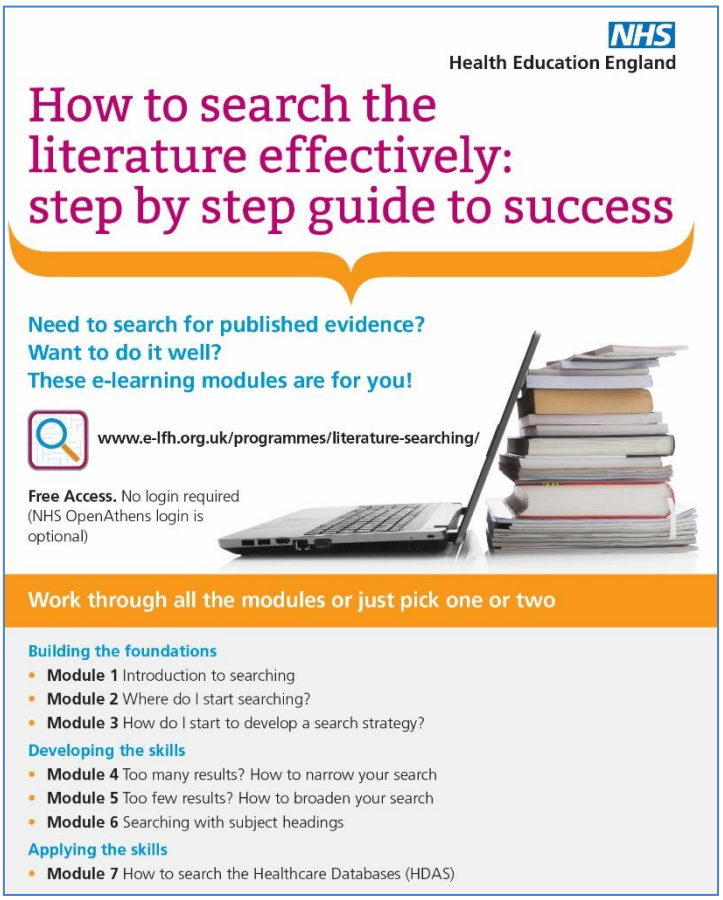

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Winter 2017/2018

- **JANUARY**

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Thursday 25th 2:00pm — 3:30pm Library Seminar Room 1

- **FEBRUARY**

Reflective Writing (for NMC Revalidation) – *please book in advance*
Thursday 8th 1:00pm — 2:00pm Library Seminar Room 1

Using Evidence-Based Databases – *please book in advance*
Friday 16th 1:00pm — 2:00pm Library IT Room

Critical Appraisal (Qualitative Study paper) – *please book in advance*
Tuesday 20th 2:00pm — 3:30pm Library Seminar Room 1

- **MARCH**

Undertaking RCT Research: study design basics and critical appraisal
Tuesday 6th 2:30pm — 4:00pm Library Seminar Room 1

Reflective Writing (for NMC Revalidation) – *please book in advance*
Friday 9th 12:00pm — 1:00pm Library Seminar Room 1

Using Evidence-Based Databases – *please book in advance*
Thursday 15th 12:00pm — 1:00pm Library IT Room

Critical Appraisal (Cohort Study paper) – *please book in advance*
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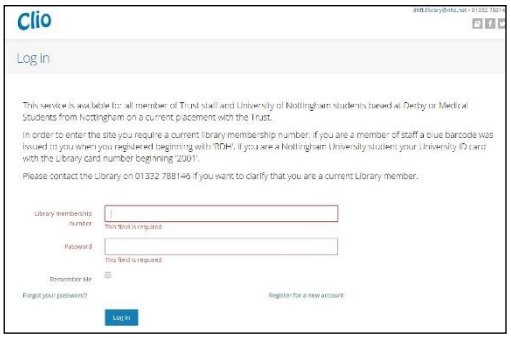

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