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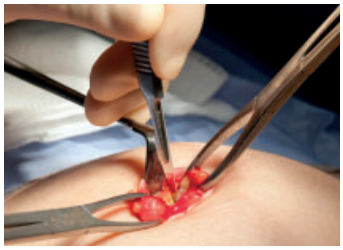

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ORIGINAL RESEARCH Systematic review and pairwise and network meta-analysis

Dipeptidyl peptidase-4 inhibitors and gallbladder or biliary disease in type 2 diabetes

He L, Wang J, Ping F, et al

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Study question What is the effect of dipeptidyl peptidase-4 (DPP-4) inhibitors on gallbladder or biliary diseases?

Methods This systematic review and pairwise and network meta-analysis included randomised controlled trials of adults with type 2 diabetes. PubMed, EMBASE, Web of Science, and CENTRAL were searched from inception until 31 July 2021 for randomised controlled trials that compared DPP-4 inhibitors, glucagon-like peptide-1 receptor agonists, and sodium-glucose cotransporter-2 inhibitors with one another or with placebo or other antidiabetes drugs. Outcomes were a composite of gallbladder or biliary diseases, cholecystitis, cholelithiasis, and biliary diseases.

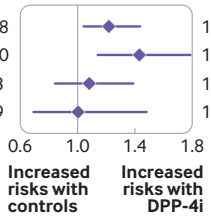
Study answer and limitations In the meta-analysis of 82 trials with 104 833 participants, DPP-4 inhibitors were significantly associated with an increased risk of the composite of gallbladder or biliary diseases (odds ratio 1.22 (95% confidence interval 1.04 to 1.43); risk difference 11 (2 to 21) more events per 10 000 person years) and cholecystitis (1.43 (1.14 to 1.79); 15 (5 to 27)) but not with the risk of cholelithiasis and biliary disease. However, the included studies were not specially designed to evaluate the effects of DPP-4 inhibitors on gallbladder or biliary diseases.

What this study adds DPP-4 inhibitors increased the risk of cholecystitis in randomised controlled trials, especially with longer treatment durations, which requires more attention from physicians in clinical practice.

Funding, competing interests, and data sharing
Full details on bmj.com.

Study registration PROSPERO CRD42021271647.

Outcomes	No of studies	No of events/total: DPP-4i groups	No of events/total: Control groups	Odds ratio (95% CI)	Odds ratio (95% CI)	ARD (95% CI) per 10 000 person years	Test of effect (P value)	τ^2	Q test (P value)
Composite of gallbladder or biliary diseases	82	338/56 005	256/48 828		1.22 (1.04 to 1.43)	11 (2 to 21)	0.02	0.027	0.88
Cholecystitis	60	173/48 231	110/43 720		1.43 (1.14 to 1.79)	15 (5 to 27)	0.002	0	0.99
Cholelithiasis	49	110/47 240	94/41 183		1.08 (0.83 to 1.39)	2 (-4 to 10)	0.58	0	0.99
Biliary diseases	28	46/37 591	42/35 309		1.00 (0.68 to 1.47)	0 (-5 to 7)	0.98	0.137	0.87



Risks of cholecystitis, cholelithiasis, and biliary disease in patients taking DPP-4 inhibitors (DPP-4i). Absolute risk difference (ARD) is number of events per 10 000 person years. Control groups=placebo or non-incretin drugs. CI=confidence interval

Airborne SARS-CoV-2

ORIGINAL RESEARCH Rapid systematic review

Long distance airborne transmission of SARS-CoV-2

Duval D, Palmer JC, Tudge I, et al
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Study question What is the potential for long distance airborne transmission of SARS-CoV-2 in indoor community settings, and what factors might influence transmission?

Methods This review employed rapid systematic methodologies to identify and critically assess evidence published up to 19 January 2022. Observational studies reporting on transmission events in indoor community (non-healthcare) settings were considered for inclusion if long distance airborne transmission of SARS-CoV-2 was the most likely route. Primary outcomes were SARS-CoV-2 infections through long distance airborne transmission (>2 m) and any modifying factors. Methodological quality of included studies was rated using the quality criteria checklist, and certainty of primary outcomes was determined using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework.

Study answer and limitations 22 reports relating to 18 studies were identified. All studies were outbreak investigations; three of them were rated as high methodological quality, five as medium, and 10 as low. Long distance airborne transmission was likely to have occurred for some or all transmission events in 16 studies and was unclear in two studies. In the 16 studies, one or more factors plausibly increased the likelihood of long distance airborne transmission occurring, particularly insufficient air replacement, directional air flow, and activities associated with increased emission of aerosols, such as singing or speaking loudly. The certainty of evidence was judged as very low for all outcomes. Although some of the included studies were well conducted outbreak investigations, they remain at risk of bias because of their design and do not always provide the level of detail needed to fully assess transmission routes.

COMMENTARY Time for an indoor air revolution

Debate over the exact mode of transmission of SARS-CoV-2 has been intense.[1] This is entirely reasonable, given that the mechanism of spread determines preventive and potentially lifesaving policies. But the choice between respiratory aerosol or droplet settled on short range droplets, which neatly circumvented any risk outside the fabled 2m zone.[1] This choice gave rise to social distancing, hand and surface hygiene, and masks, but not to improved indoor air quality.

And so the debate smoulders on, as Duval and colleagues report from their linked systematic review supporting the role of long distance airborne transmission of SARS-CoV-2.[2] The review examined covid-19 transmission events in a variety of indoor community settings ranging from fitness facilities, offices, buses, and restaurants to choir venues and a church, but not hospitals, hospices, or care homes.[2-8] The inclusion of care home outbreaks might have strengthened overall findings, along with more recent studies detailing nosocomial clusters among vaccinated healthcare workers.[9 10]

Study selection was, of necessity, somewhat labile, because any outbreak inferring even the slightest possibility of contact or fomite transmission would have been excluded. This might explain the omission of notable community outbreaks,[11-13] including those where the virus almost certainly spread through sanitation systems in high rise flats.[14 15] This opportunistic transmission route is reminiscent of the notorious Amoy Gardens outbreak of SARS-1 in Hong Kong.[16]

Toilet aerosols

SARS-CoV-2 survives in faeces, urine, and waste water, and aerosol transmission through interconnected sanitary drains (just as for SARS-1) needs further exploration.[17] Viral spread in toilet facilities might not feature in the literature, but that does not mean the risk should be ignored. Faecal aerosols might have played an important role in transmission during the covid-19 pandemic, especially as diarrhoea is common among infected patients and viral shedding persists in stool despite negative respiratory sample results.[17 18]

Arguably, Duval and colleagues' review should also have mentioned studies reporting aerosol transmission of SARS-CoV-2 between animals.[19-21] Given that similar studies on humans would never obtain ethical approval, these investigations—which virtually all support long distance aerosol spread, skilfully emulate the original work on tubercle transmission from the early 1960s.[22 23] This work was eventually accepted by the scientific community as evidence for airborne transmission of tuberculosis in humans—despite the fact that *Mycobacterium tuberculosis* has never been successfully cultured from air. It is hoped that SARS-CoV-2 and its proclivity for airborne transmission will be accepted a little quicker than it was for tuberculosis. Influenza might have to wait.[22]

We really should not have to wait for randomised evidence that might never materialise

Of course, some argue that reliance on observational events is poor science. But a role clearly exists for detailed epidemiology in respiratory outbreaks, simply because it provides empirical validation that aerosol transmission occurs, and in fact occurs extensively.[22] As Duval and colleagues surmise, there is a need to develop a new framework for evidence synthesis of outbreak investigations.[2-25]

Either that, or more than a century of detailed epidemiological work identifying the cause of disease outbreaks and tracking the spread of notable pathogens must be ignored. After all, who would choose to inhabit the "control" environment in a randomised trial examining the protective effect of fresh air during an influenza outbreak?[26] It is laudable to seek solid

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What this study adds This rapid systematic review found evidence suggesting that long distance airborne transmission of SARS-CoV-2 might occur in indoor settings such as restaurants, workplaces, or choir venues, and identified factors such as insufficient air replacement that probably contributed to transmission. These results strengthen the need for mitigation measures in indoor settings, particularly adequate ventilation.

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Systematic review registration PROSPERO CRD42021236762.

scientific evidence, but when a disease spreads so rapidly, we really should not have to wait for randomised evidence that might never materialise.[27]

Just as the world woke up to a pandemic, a small group of determined scientists (including this author) appealed for consideration of airborne spread.[28] Their advice was summarily dismissed.[1] And so the group—in common with the pioneers of tuberculosis transmission—"provided an ingredient that scientists seldom mention: a mission to convince unbelievers."[29]

Now, the evidence presented in Duval and colleagues' review, tenuous as it is, validates the premise that tiny respiratory particles containing SARS-CoV-2 freely transmit throughout inadequately ventilated environments. That this small group of scientists have (almost) won their argument is of small consolation to those still experiencing the effects of covid-19. But through persistence and escalating independent evidence, better indoor air quality can be entertained for everyone in the future.[30]

It is hoped that public health leaders will develop practical guidance and "tilt" people and places closer to safety.[31] Now, indeed, is the time for an indoor air revolution.[32 33]

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MARK BETON/ALAMY

User centered clinical decision support to implement initiation of buprenorphine for opioid use disorder in the emergency department

Melnick ER, Nath B, Dziura JD, et al

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Study question Can a user centered clinical decision support tool increase rates of initiating buprenorphine in the routine emergency care of individuals with opioid use disorder?

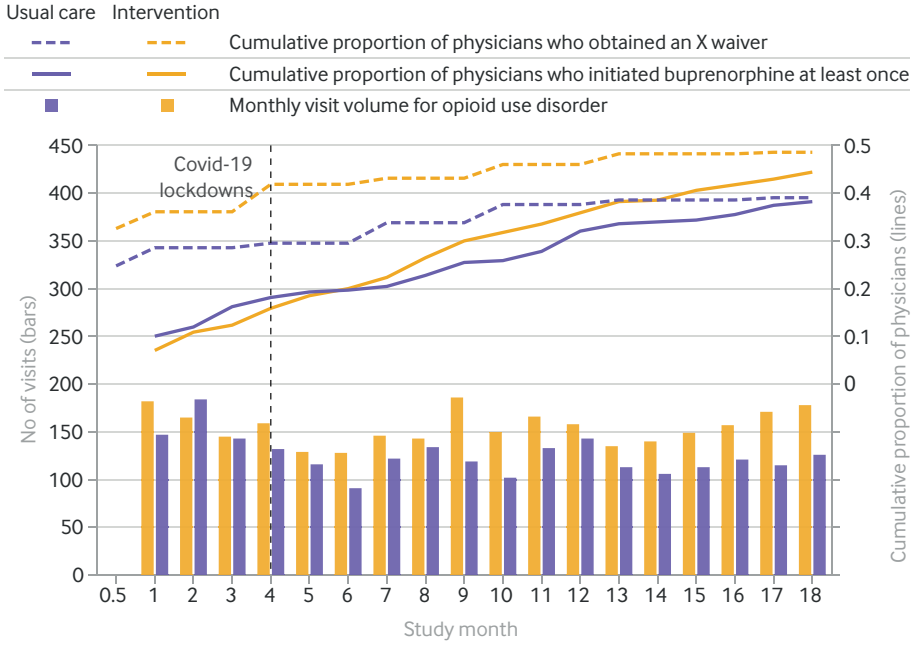
Methods A parallel group randomized pragmatic trial with emergency department clusters allocated to intervention versus usual care was performed in 18 emergency department clusters across five healthcare systems in the US. 1 413 693 visits to the emergency department from 1 November 2019 to 31 May 2021 were assessed for eligibility, resulting in 5047 patients with opioid use disorder under the care of 599 attending physicians for analysis. The intervention was a user centered, physician facing clinical decision support system integrated into the electronic health record to support initiating buprenorphine in the emergency department by helping clinicians to diagnose opioid use disorder, assess the severity of withdrawal, motivate patients to accept treatment, and complete electronic health record tasks by automating clinical and after visit documentation, order entry, prescribing, and referral. The primary outcome was the rate of initiation of buprenorphine (administration or prescription of buprenorphine) in the emergency department among patients with opioid use disorder.

Study answer and limitations The EMBED (EMergency department initiated BuprenorphinE for opioid use Disorder) intervention did not affect the rate of patients receiving buprenorphine in the emergency department (primary outcome) compared with usual care (adjusted generalized estimating equations odds ratio 1.22, 95% confidence interval 0.61 to 2.43, P=0.58). However, EMBED was associated with a higher proportion of physicians initiating buprenorphine at least once during the trial in the intervention arm compared with the usual care arm (44.4% *v* 34.0%, P=0.01). When EMBED was used, it was associated with high rates of initiation of buprenorphine. The study had sampling bias and misclassification bias related to limitations of data collection.

What this study adds The EMBED intervention did not increase rates of initiation of buprenorphine in the emergency department but the number of unique physicians that provided buprenorphine in the emergency department and prescribed naloxone increased in the intervention arm. Although streamlining and automating electronic workflows can potentially increase adoption of complex, unfamiliar evidence based practices, more interventions are needed to address other barriers to treatment of addiction and increase the rate of initiating buprenorphine in the emergency department in patients with opioid use disorder.

Funding, competing interests, and data sharing
Supported by the National Institute on Drug Abuse of the National Institutes of Health. No competing interests declared. A de-identified participant dataset with an associated data dictionary will be publicly available at www.icpsr.umich.edu/web/pages/NAHDAP/index.html.

Trial registration ClinicalTrials.gov NCT03658642.



Temporal trends in visits to the emergency department for opioid use disorder and cumulative proportion of physicians who initiated buprenorphine at least once during the trial and obtained an X waiver to prescribe buprenorphine by study arm (intervention or usual care). Monthly visits for opioid use disorder is charted by study arm. An interactive version of this graphic is available at https://bit.ly/3NvGulj