Pharmacological treatment of opioid-induced constipation: moving ahead to new targets

We read with great interest the systematic review and network meta-analysis on pharmacological treatments for opioid-induced constipation (OIC).[1] Based on 27 randomised controlled trials (RCTs, 9149 patients), the authors concluded that peripherally acting mu-opioid receptor antagonists (PAMORAs) and the prokinetic prucalopride were all more effective than placebo for OIC and that naloxone and naldemedine were the most efficacious ones.[1]

We have previously documented that OIC has high prevalence and is associated with reduced quality of life (QoL) in opioid-addicted patients treated with opioid substitution treatment (OST).[2] Overweight is also common and interventions for weight loss are recommended in patients under OST.[3] Orlistat, a weight-control drug that inhibits lipase, thereby decreasing fat absorption from the intestinal lumen, has been reported to improve drug-resistant constipation in small case series,[4 5] and clozapine-induced constipation in a small RCT.[6]

In an open-label observational study, we explored whether orlistat may improve OIC in OST patients. From a cohort of 1057 heroin-dependent patients under OST previously reported,[2] we recruited patients with OIC, who were prescribed orlistat 60 mg three times a day for weight reduction. OIC was measured with the Wexner Constipation Scoring System (WCSS),[2] Patient Assessment of Constipation (PAC) Symptom questionnaire (PAC-SYM), Bowel Function Index (BFI)[7] and the bowel movements (BMs) per week. QoL related to OIC was assessed with the PAC QoL questionnaire (PAC-QOL).[7] Outcome measures were assessed before starting orlistat (T0) and after 2 months of treatment (T1).

We recruited 20 patients (20 men, mean age 43.8±5.4) under OST (methadone: n=19, mean daily dose 85.3±67.2 mg; buprenorphine: n=1, daily dose 8 mg). Comorbidities included smoking (n=16), hypertension (n=6), epilepsy (n=3), hypothyroidism (n=2), alcoholism (n=2) and diabetes (n=1). Concomitant drugs were benzodiazepines (n=15), neuroleptics (n=4), antidepressants (n=6) and gabapentin (n=1). WCSS (Wilcoxon signed-rank test, p<0.001; figure 1A), PAC-SYM (p<0.001; figure 1B), BFI (p<0.001; figure 1C), PAC-QOL (p<0.001; figure 1D), PAC-QOL Satisfaction (p<0.001; figure 1E), BMs per week (p<0.001; T0: ≤2 in all patients, T1: ≥3 in 16 patients, increase ≥1 from T0 in 18; figure 1F) and body mass index (T0: median 30.3, IQR 27.8–33; T1: 29.0, 26.2–31.4; p=0.001) significantly improved at T1 versus T0. PAC-QOL Satisfaction at T1 was excellent (n=9), good (n=8), fairly good (n=2) and poor (n=1). The side effects were transitory and included diarrhoea (n=8) that required tapering to two times a day (n=4, two returned to three times a day after a week) and one a day (n=1), stomach distress (n=2), steatorrhoea (n=1) and nausea (n=1), but no patient stopped the treatment.

Our findings suggest that orlistat, through decreased fat absorption from intestinal lumen and steatorrhoea, may improve OIC in patients under OST. In accordance with previous studies, the

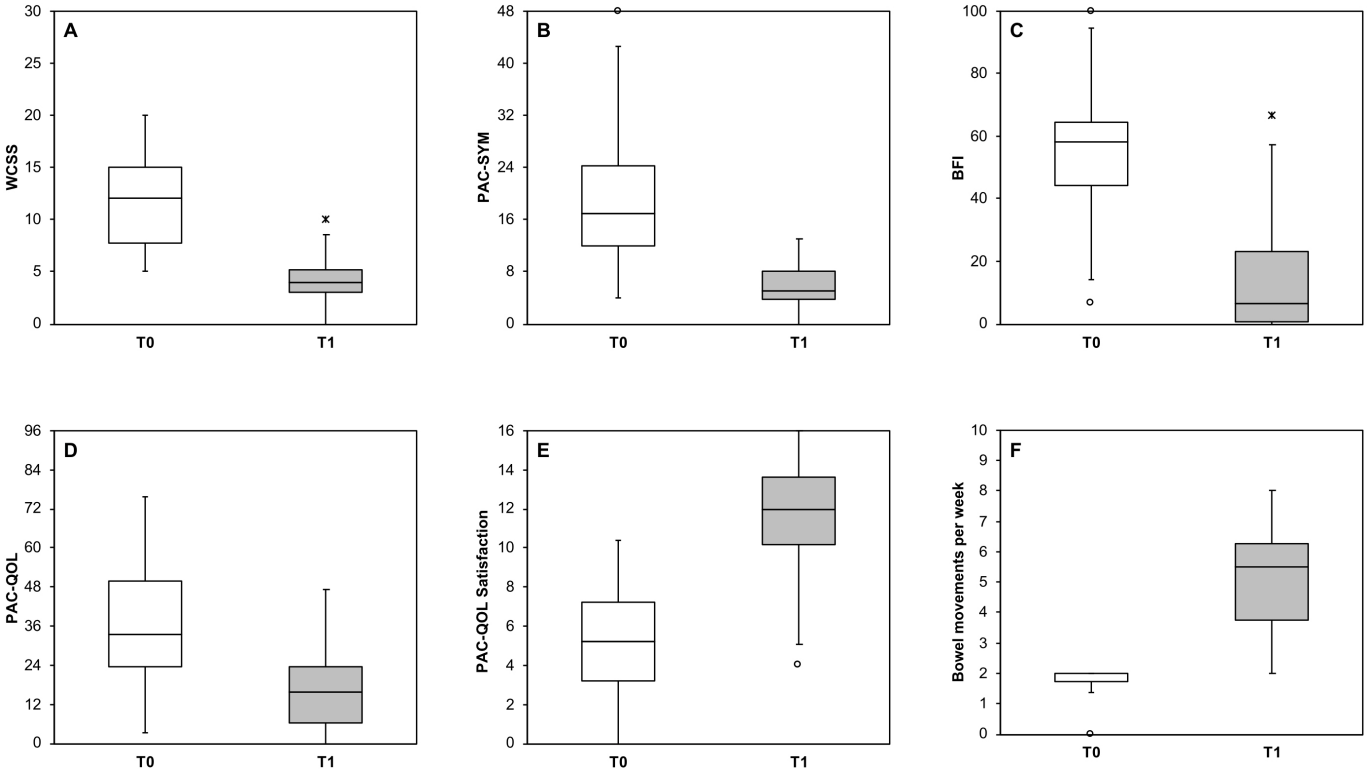

Figure 1 Outcome measures at baseline (T0) and after 2 months (T1). Box and whiskers plots show constipation outcomes for the 20 patients. (A) Wexner Constipation Scoring System (WCSS, range 0–30). (B) Patient Assessment of Constipation Symptom questionnaire (PAC-SYM, range 0–48). (C) Bowel Function Index (BFI, range 0–100). (D), (E) Patient Assessment of Constipation Quality of Life (PAC-QOL; range 0–96; satisfaction: 0–16). (F) Number of bowel movements per week. Higher scores indicate worse outcomes for BFI, PAC-QOL, PAC-SYM and WCSS. Higher score indicates better outcome for PAC-QOL satisfaction.

effect on weight reduction was modest.[8] Most patients achieved ≥3 BMs per week at T1 (80%), increase ≥1 from T0 (90%), and 85% of them reported fairly good-to-excellent satisfaction to orlistat, while <50% of patients with OIC report satisfactory effect to laxatives.[1 9]

The main limitations of our study are the open-label observational design, small sample size and short duration impeding to document side effects to long-term treatment. Moreover, OST patients may not represent the wider population of patients under opioids with OIC. Future RCTs should explore whether orlistat can be more effective than PAMORAs in OIC, improve constipation unrelated to opioids and offer information on side effects and cost-effectiveness profile.

Fabio Lugoboni,[1] Federico Vignoni,[1] Stefano Tamburin ,[2] Gruppo InterSERT di Collaborazione Scientifica (GICS)

[1]Department of Medicine, Addiction Medicine Unit, Integrated University Hospital of Verona, Verona, Veneto, Italy
[2]Department of Neurosciences, Biomedicine & Movement Sciences, University of Verona, Verona, Italy

Correspondence to Professor Stefano Tamburin, Department of Neurosciences, Biomedicine & Movement Sciences, University of Verona, Verona 37134, Italy; stefano.tamburin@univr.it

Collaborators Gruppo InterSERT di Collaborazione Scientifica (GICS): V Arcarese, C Arzillo, L Benigna, N Bersani, P Bersani, C Biasin, C Bossi, A Bottazzo, A Bove, E Caccamo, S Cancian, F Cantanchin, D Cantiero, G Canzian, D Cargnelutti, D Casalboni, R Casarini, M Cibin, P Civitelli, T Cozzi, L De Cecco, R Del Zotto, F Dersini, I Duranti, M Fadelli, E Favero, N Fontana, A Franceschini, M Gaiga, M Gardiolo, N Gentile, D Gervino, N Ghezzo, M A Giacomin, H Kashanpour, M Mazzo, D Meneghello, C Mihalcea, E Milan, M Montresor, E Moratti, A Pani, V Pavani, P Pellachin, F Peroni, M Piazza, M Pieri, D Prosa, M Residori, P Righetti, M A Ripoli, P Riscica, C Rizza, V Rizzetto, A Rossi, A Rovea, A Ruffato, C Ruzziconi, R Sabbion, E Santo, M Scarzella, N Sembianti, P Simonetto, C Smacchia, M Stellato, C Stimolo, L Suardi, A Vaiana, V Zavan, E Zerbetto, M Zerman.

Contributors FL: conception and design of the study, review of the literature, review and editing of the manuscript. FV: design of the study, data collection, review and editing of the manuscript. ST: conception and design of the study, review of the literature, statistical analysis, writing the manuscript. All the authors read and approved the final version of the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval The study protocol was approved by the Ethics Committee of the Verona University Hospital, Verona, Italy (approval ID 533CESC).

Provenance and peer review Not commissioned; internally peer reviewed.

To cite Lugoboni F, Vignoni F, Tamburin S, *et al*. *Gut* 2020;**69**:2264–2265.

Received 4 January 2020
Revised 4 March 2020
Accepted 12 March 2020
Published Online First 24 March 2020

Gut 2020;**69**:2264–2265. doi:10.1136/gutjnl-2020-320602

ORCID iD
Stefano Tamburin http://orcid.org/0000-0002-1561-2187

REFERENCES

1 Luthra P, Burr NE, Brenner DM, *et al*. Efficacy of pharmacological therapies for the treatment of opioid-induced constipation: systematic review and network meta-analysis. *Gut* 2019;68:434–44.
2 Lugoboni F, Mirijello A, Zamboni L, *et al*. High prevalence of constipation and reduced quality of life in opioid-dependent patients treated with opioid substitution treatments. *Expert Opin Pharmacother* 2016;17:2135–41.
3 Sason A, Adelson M, Herzman-Harari S, *et al*. Knowledge about nutrition, eating habits and weight reduction intervention among methadone maintenance treatment patients. *J Subst Abuse Treat* 2018;86:52–9.
4 Guarino AH. Treatment of intractable constipation with orlistat: a report of three cases. *Pain Med* 2005;6:327–8.
5 Iqbal F, Samuel M, Tan EJK, *et al*. Letter: orlistat as a potential treatment for chronic idiopathic constipation. *Aliment Pharmacol Ther* 2016;43:848–9.
6 Chukhin E, Takala P, Hakko H, *et al*. In a randomized placebo-controlled add-on study orlistat significantly reduced clozapine-induced constipation. *Int Clin Psychopharmacol* 2013;28:67–70.
7 Olesen AE, Drewes AM. Validated tools for evaluating opioid-induced bowel dysfunction. *Adv Ther* 2011;28:279–94.
8 Khera R, Murad MH, Chandar AK, *et al*. Association of pharmacological treatments for obesity with weight loss and adverse events: a systematic review and meta-analysis. *JAMA* 2016;315:2424–34.
9 Candy B, Jones L, Larkin PJ, *et al*. Laxatives for the management of constipation in people receiving palliative care. *Cochrane Database Syst Rev* 2015;5:CD003448.