

to use it with caution, in a dose never exceeding 600 mg, once a day, in patients with MDR- and XDR-TB, who have few other drug options. All of our patients were given written instruction on the side-effects that they are likely to encounter and, at each follow-up, these were diligently checked for. In all patients treated with linezolid, clinical, haematological and neurological evaluations are mandatory on a monthly basis, as well as frequent ophthalmological tests.

To conclude, the high frequency of adverse effects to linezolid warrants extreme caution when this drug is used for prolonged periods of time in MDR-TB patients. Thus, prospective, randomised and multicentre evaluations are needed in order to test the efficacy of linezolid as well as the short- and long-term tolerability of the drug in TB patients.

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From the authors:

We read with much interest the letter by Z.F. Udawadia and co-workers reporting interesting data on the Indian experience in the treatment of multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis (TB) with linezolid.

Murine studies performed a decade ago demonstrated efficacy of linezolid and other oxazolidinones against *Mycobacterium tuberculosis* [1], despite its low early bactericidal activity [2].

Few clinical reports on selected case series have been made available in the recent past for this specific, presently off-label, indication [3–6]. The profile of this drug in the treatment of MDR-/XDR-TB is at present low, as it is included in Group 5, *e.g.* the group of drugs with limited or substantially unknown activity against *M. tuberculosis* [7, 8].

Preliminary evidence indicated a high toxicity profile for its long-term use at the dose of 600 mg *b.i.d.*, as up to 25–45% of cases reported severe anaemia and/or thrombocytopenia and peripheral and optic neuropathy [3–6]. The use of the drug is also limited by its high cost, being in the order of €100 per vial in Western Europe.

The *European Respiratory Journal* has recently become a forum for discussing potentialities of this drug in the treatment of MDR-/XDR-TB cases by publishing the TBNET (Tuberculosis Network European Trials group) study on 85 cases [5] performed in four European countries (including Belarus in Eastern Europe), the Indian experience presented by Z.F. Udawadia and co-workers from Mumbai, India of 18 cases, and the two case reports of YEW *et al.* [9] regarding the use of linezolid 800 mg *q.d.*

The aim of the present study is to discuss the key findings of the TBNET [5] and Indian studies and to draw further conclusions, focusing on the available evidence on linezolid safety.

The table included in the study by Z.F. Udawadia and co-workers was revised, including a statistical comparison between the main results of the two studies whenever possible.

Data were analysed using Stata 9.0 (StataCorp, College Station, TX, USA). Comparisons between proportions were performed using the Chi-squared test; unpaired t-tests were used for continuous variables when appropriate. Differences were considered to be significant when $p < 0.05$.

The comparison between the two studies suggests the following three main conclusions.

Representativeness and study design: the study by Z.F. Udawadia and co-workers was performed at a single tertiary hospital in India, whereas the study by MIGLIORI *et al.* [5] included patient data from more than 20 hospitals in four European countries. Genetic differences between the patient populations could have a role in explaining the different proportions of adverse events found in the two studies. While the European study was retrospective, the Indian one is prospective, allowing for collection of more variables, including, for example, body weight. This allowed the calculation of the body mass index and discussion of the potential role played by malnutrition in increasing the proportion of cases facing adverse events.

Drug dosage, treatment duration and adverse events: the duration of linezolid treatment was longer in the Indian than in the European study (table 1). 600 mg *q.d.* was prescribed in the Indian study, while either 600 or 1,200 mg was used in the European one. While in the European study the patients who were prescribed 600 mg had significantly fewer major adverse events (14.3%), in the Indian study, at the same dosage, the proportion of major side effects was significantly higher than that of the overall sample in Europe (61% *versus* 40.4%; $p < 0.001$) (table 1). While in Europe anaemia was the main

TABLE 1 Comparison of epidemiological and clinical features of the TBNET cohort (MIGLIORI *et al.* [5]) and the Udwadia cohort

Variables	TBNET cohort	Udwadia cohort	p-value
Sample size n	Safety 85, Efficacy 45 LZD treated vs 110 non-LZD treated	18 LZD treated	
Males	33/45 (73.3%) LZD treated	36/78 (46.2%) LZD treated	0.004
HIV seropositive	7/155 (4.5%)	Unknown	
LZD arm	85/195	18/78	0.005
MDR-TB	41/45 (91.1%)	11/18 (61.1%)	
XDR-TB	4/45 (8.9%)	7/18 (38.8%)	
Mean ± sd LZD administration time days	222 ± 249	618 [#]	
Safety (AE)	600 mg <i>q.d.</i> , 4/28 (14.3%); 600 mg <i>b.i.d.</i> , 23/57 (40.4%)	600 mg <i>q.d.</i> , 11/18 (61%)	0.0009

TBNET: Tuberculosis Network European Trials; LZD: linezolid; MDR: multidrug-resistant; XDR: extensively drug-resistant; TB: tuberculosis; AE: adverse event. [#]: standard deviation unknown.

adverse event (44%), in India 38.9% of the cases reported peripheral neuropathy. The time interval between linezolid prescription and adverse events appearance was similar in the two studies. Further attention is required to define the efficacy/safety profile of a dosage of linezolid 800 mg *q.d.* in the treatment of “complicated” MDR/XDR-TB cases [9].

Outcomes: a complete comparison on outcomes is not possible, as the time to sputum smear and culture conversion was not calculated in the study by Z.F. Udwadia and co-workers. The treatment success is, overall, of the same order of magnitude (71% in Europe and 61% in India). Both studies reported nonsignificantly different outcomes between regimens including and not including linezolid. In the European study [5] the results were in favour of the linezolid-treated group only for cases harbouring strains resistant to seven drugs or more. Both studies are probably biased by the absence of a randomised design: clinicians were more prone to prescribe linezolid to the most severe cases. This is why evidence on the effectiveness of linezolid is substantially indirect, *e.g.* same results achieved in more severe cases [5].

Further information on the quality of the generic products used in India will be also useful to fully understand the reasons why more major adverse events have been observed in India than in Europe or in the USA. An American study confirmed recently the good safety profile of the 600 mg daily dose of linezolid: adverse events occurred in nine out of 30 patients (30%) [10].

Genetic reasons, as well as malnutrition, are among the possible co-factors able to explain these differences.

In conclusion, once more, the main message arising is that we need well-designed, randomised and controlled clinical trials to better understand the potentialities of linezolid in the treatment of MDR-/XDR-TB cases [8–11].

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The online Cough Clinic

To the Editors:

The recent paper by DETTMAR *et al.* [1] describes an important way in which patients with chronic cough (and their general practitioners) can obtain information online as to the probable diagnosis of their coughs and the preferred treatment.

The only three possible diagnoses are reflux (gastro-oesophageal reflux (GOR)), asthma and rhinitis (post-nasal drip syndrome (PNDS)).

We tested the questionnaire with histories of four patients. They had respectively post-viral, cigarette smoking, habit (Tourette's) and upper respiratory tract infection cough. Each was diagnosed as probable GOR.

The paper raises a number of important questions. First, the paper lists 16 questions pointing to the probable diagnoses, which are identified for each question. However, the current online questionnaire (November 2009) adds a further five questions with no indication of the diagnoses they point to, surely essential information. Presumably this change in the questionnaire was made after the paper was submitted, but it means that the results described in the paper cannot be added to any results from the "new" online questionnaire.

Secondly, how "specific" are the questions? For example, can we be certain, as the questionnaire is, that "clearing your throat" points to GOR and that "excess mucus in the throat" points to PNDS? In the printed questionnaire, if the symptoms are in the throat, four questions point to GOR and two point to PNDS, so there may be a bias towards GOR.

Thirdly, we are told that the questions are not weighted in favour of a particular diagnosis, in that adjustments are made for the different numbers of questions pointing to each diagnosis. But we are also told that there are weighting factors for individual questions, but we are not given these. Within each of the three probable diagnoses, what does this mean? For GOR, does cough during or after eating, point more (or less) than clearing the throat, both of which indicate GOR? For asthma, does wheezing have a greater weighting factor than cough on waking? These examples could be multiplied.

Fourthly, the use of the Likert scale may be justified, but it raises well-known problems. It gives a linear output to a nonlinear input that is different for each question. A mild sensation of heartburn is probably as predictive of GOR as a strong sensation but this may not be true of throat clearing. In other words, there should be adjustments within the scales as well as between them. Were these adjustments considered and made and, if so, what were they?

Fifthly, figures 2 and 3 in the paper give the proportions of patients reporting each of the 16 symptoms. For asthma diagnosis, answers to the selected three questions show a strong preponderance for those subjects "probably having asthma". For PNDS diagnosis, the answers to the selected five questions show a similar strong preponderance for patients "probably having PNDS". This is to be expected. It follows that all the other patients must probably have GOR. But if you look at the eight GOR-pointing questions, each of them shows roughly equal proportions of patients finally diagnosed with GOR, asthma or PNDS. In other words, the questions for GOR are very non-specific (and lack diagnostic value), unlike those for asthma and PNDS. GOR is the diagnosis after eliminating those who have strong signs of asthma or PNDS; and no other causes of chronic cough are recognised.

Sixthly, the current online version asks 21 questions, each with scores 0–5 (total 105). If someone answers 1 to one question only (total 1 out of 105) he will be given a diagnosis based on a minimal input. Our "habit cough" patient had a total score of 1 ("very mild hoarse voice"), <1% of the possible total and was confidently told that she probably had GOR. We need to be told the probabilities of the probable diagnoses in order to assess the method. Additionally, since only 12.4% of the patients responded to the follow-up questionnaire, it will never be possible to determine its validity.

Seventhly, it is a pity that the "validation study" included only 30 patients and that it was conducted at the home of the chronic cough questionnaire, with probably much the same questions but asked verbally, rather than independently.

Eighthly, we are told on the website that 78.39% of those who replied to the follow-up questionnaire found that it had "helped their condition". Since only 944 (9.7%) out of 9,709 patients replied to the follow-up, we don't know whether the other 90.3 % were "helped". We don't know if the 9.7% were representative and many chronic coughers get better anyway. There were no control groups.

Finally, we are told that the questionnaire is based on the reports of two ERS Task Forces on Cough. The second Task Force [2] scarcely mentions diagnostic questions and the first [3] gives diagnostic signs and symptoms for different causes of chronic cough (as does any textbook) but nowhere evaluates them. (The authors of this letter were members of both Task Forces.)

These are examples and pressure on space may have prevented including this information and its discussion in the paper but they are crucial for interpretation of the results and could have been presented in the online supplement.