

scheme comes with good tolerability of the drugs. The strategies to block the effects of tumour necrosis factor- α seem to be effective also in extremely severe cases of psoriasis that are resistant to other therapeutic regimens. Numerous other biologics are in advanced phases of clinical development. These employ at least one of four strategies, namely reduction of pathogenic T cells denileukin difitox, inhibition of T cell activation and migration (efalizumab), correction of cytokine deviation (interleukin 10), or blocking pro-inflammatory cytokines (ABX-IL-8).¹⁰

Biologics are still not perfect drugs. They come with an enormous prize tag, resulting in annual costs for treatment of around €10 000 (£6894; \$10 827) per patient per year. Moreover, only a minority of patients (about a third) experience a dramatic and fast clinical improvement when taking these drugs (with the exception of infliximab), whereas others respond rather slowly and moderately, and some do not respond at all. It will be therefore particularly important to develop strategies to identify patients who can expect to benefit from these drugs. Finally, since many of these immunomodulatory compounds still should be considered immunosuppressive, increased risks of infection and reactivation of tuberculosis¹¹ or some lymphomas¹² must be considered in determining the long term safety of these agents.

Biologics have defined modes of action developed by purpose rather than found by chance and will make many patients not qualifying for established systemic treatments eligible to receive exactly this. Understanding their exact mechanisms of action provides the basis for rationally designed rather than empirically generated strategies for combination therapies. On the other hand—with the exception of infliximab—only subgroups of patients with psoriasis show moderate clinical improvement.¹³ The long term safety profile of biologics still needs to be established. Promising new biologics are on the horizon.¹⁴

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Comparing cannabis with tobacco—again

Link between cannabis and mortality is still not established

A recent editorial in this journal implied that as many as 30 000 deaths in Britain every year might be caused by smoking cannabis.¹ The authors reasoned that since the prevalence of smoking cannabis is about one quarter that of smoking tobacco the number of deaths attributable to smoking cannabis might be about one quarter of the number attributed to tobacco cigarettes (about 120 000). The idea that the use of cannabis increases mortality is worthy of closer examination. How do we assess this issue?

Firstly, we need to examine published data regarding use of cannabis and mortality. These data come from two large studies. The first study done in a cohort of 45 450 male Swedish conscripts, age 18-20 when interviewed about the use of cannabis, reported no increase in the 15 year mortality associated with the

use of cannabis after social factors were taken into account.² The second study was performed in a cohort of 65 171 men and women age 15-49, who were members of a large health maintenance organisation in California, United States. They completed a questionnaire assessing their use of cannabis, and reported no increase in mortality associated with use of cannabis over an average of 10 years of follow up, except for AIDS related mortality in men.³ A detailed examination showed that the mortality link between cannabis and AIDS was not a causal one. Thus published data do not support the characterisation of cannabis as a risk factor for mortality.

Secondly, we need to consider the time course of exposure to cannabis and its potential relation to mortality. No acute lethal overdoses of cannabis are

known,⁴ in contrast to several of its illegal (for example, cocaine) and legal (for example, alcohol, aspirin, acetaminophen) counterparts. Deaths due to chronic diseases resulting from substance misuse generally result from the use of that substance (for example, tobacco and alcohol) over a long time. Importantly, and in contrast to users of tobacco and alcohol, most cannabis users generally quit using cannabis relatively early in their adult lives. The table shows observations from the 1998 US national household survey on drug abuse regarding the prevalence of current (past month) use of alcohol, tobacco cigarettes, and use of cannabis among young adults (age 18-25) and older adults (age 35 or older).⁵

Percentage reporting use of alcohol, tobacco cigarettes, and cannabis in 18-25 and 35+ years age groups, 1998⁵

Age (years)	Alcohol (%)	Tobacco cigarettes (%)	Cannabis (%)
18-25	60.0	41.6	13.8
35+	53.1	25.1	2.5

The proportion of older adults who use cannabis is only 18% that of younger adults, much lower than the comparable proportions for alcohol (89%) and tobacco cigarettes (60%). Moreover since the use of cannabis in young adults declined steadily between 1979 and 1998, whereas use in older adults remained stable, the observed low prevalence in older adults is unlikely to increase in the foreseeable future. Therefore, even diseases that might be related to long term use of cannabis are unlikely to have a sizeable public health impact because most people who try cannabis do not become long term users. This observation is relevant to lung cancer, which, although strongly related to cigarette smoking, typically only occurs after at least 20 years of smoking.⁶ Also, a typical regular cannabis user smokes the equivalent of one marijuana cigarette or less per day,⁷ whereas consumption of 20 or more tobacco cigarettes is common. Exposure to smoke is therefore generally much lower in cannabis than in tobacco cigarette smokers, even taking into account the larger exposure per puff.⁸

A third issue to consider is the potential relation of the use of cannabis to diseases that contribute the most to total mortality. For example, in the United States and the United Kingdom the leading cause of death is diseases of the heart, predominantly coronary heart disease, which is strongly associated with smoking tobacco cigarettes and accounts for nearly one third of all deaths. Mittleman et al noted the quadrupling of risk found in one study when cannabis was smoked within one hour before a myocardial infarction.⁹ However, since only 0.2% of the patients with myocardial infarction reported this exposure the number of myocardial infarctions attributable to the use of cannabis is extremely small. Cannabis does not contain nicotine, a component of tobacco that contributes importantly to the risk of coronary heart disease. Use of cannabis in a young adult population was not associated with the presence of calcium in coronary arteries—an indicator of coronary atherosclerosis¹⁰—and a cohort study conducted in a large health maintenance organisation showed no association between the use of cannabis and

admission to hospital for myocardial infarction and all coronary heart disease.¹¹

Two caveats must be noted regarding available data. Firstly, the longer term follow up of cohorts of cannabis users may still show an increased risk of cancers, chronic diseases, and mortality if enough members of the study cohort continue to smoke cannabis often enough and for long enough. The cohorts to date have not followed cannabis smokers into later adult life so that it might be too early to detect an increased risk of chronic diseases that are potentially associated with the use of cannabis. Secondly, the low rate of regular use of cannabis and the high rates of discontinuation during young adulthood in the United States may reflect the illegality and social disapproval of the use of cannabis. This means that we cannot assume that smoking cannabis would continue to have the same small impact on mortality (as it probably does with current patterns of use) if its use were to be decriminalised or legalised.

Although the use of cannabis is not harmless, the current knowledge base does not support the assertion that it has any notable adverse public health impact in relation to mortality. Common sense should dictate a variety of measures to minimise adverse effects of cannabis. These include discouraging the use by teenagers, who seem to be most at risk of future problems from drug use,¹² not using before or during the operation of automobiles or machinery, not using excessively, and cautioning in people with known coronary heart disease.

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