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Clinical toxicological aspects of fluoroquinolones

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Abstract

Reactions of the gastrointestinal tract and the central nervous system are the most often observed adverse effects during therapy with fluoroquinolones. Pathogenesis of the *neurotoxic effects* of fluoroquinolones could be related to the activation of the NMDA receptor. Animal experiments as well as clinical experience show that the *cardiotoxic potentials* of sparfloxacin and grepafloxacin are higher than those of the other fluoroquinolones: they cause QT prolongation at rather low doses thus increasing the risk for severe arrhythmia (torsades de pointes). *Phototoxicity* has been described for all quinolones, but derivatives with a halogen atom at position 8 show the highest potential for such reactions (e.g. clinafloxacin). *Chondrotoxicity* of quinolones can affect the articular cartilage and the epiphyseal growth plate in immature animals; the use of these drugs in pediatrics should be restricted to carefully selected indications (such as the use of ciprofloxacin in cystic fibrosis). Tendinitis and *tendon ruptures* can also be induced by quinolones. Overall, quinolones are as well tolerated as most other anti-microbial agents. However, their specific toxic potentials have to be considered when they are chosen for treatment of bacterial infections.

Keywords: Fluoroquinolones; Toxicity; Antimicrobial therapy

1. Introduction

Quinolones are widely used anti-bacterial agents. The development of these drugs started with the non-fluorinated drug nalidixic acid in the early 1960s and proceeded in the 1980s to the first 6-fluorinated derivatives with enhanced activity against Gram-negative bacteria (e.g. norfloxacin, ofloxacin, ciprofloxacin). At that time, it was generally believed that fluorination is essential in obtaining drugs with high anti-bacterial activity. Further fluoroquinolones with improved activity against Gram-positive bacteria (moxifloxacin, gatifloxacin) have come to therapeutic use during the last few years. Recently, highly active quinolones have been developed which are *not* fluorinated in position 6, but bear fluorine atoms at the side chain (e.g. BMS-284756) or are non-fluorinated derivatives (e.g. PGE9262932). Thus, in future it might be reasonable to avoid the term fluoroquinolones and to call these drugs more generally 'quinolones' again, although they differ considerably from the classic drugs such as nalidixic acid. With the given multiplicity of quinolones, it is necessary to group them according to their features in different classes as has been proposed by the Paul–Ehrlich-Society of

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Table 1
Widely used fluoroquinolones grouped according to the PEG classification

Class	Fluoroquinolone	Spectrum/therapeutic use
I	Norfloxacin	Mainly active against Gram-negative pathogens, almost exclusively used for urinary tract infections
II	Ofloxacin Ciprofloxacin	Broad indications for systemic use, but moderate activity against Gram-positive pathogens
III	Levofloxacin [a]	Improved activity against Gram-positive and 'atypical' pathogens, infections of the respiratory tract and others
IV	Moxifloxacin	Improved activity against Gram-positive and 'atypical' pathogens as well as anaerobes, infections of the respiratory tract and others
	Gatifloxacin	

[a] Levofloxacin is the L-enantiomer of the racemate ofloxacin, its activity is approximately twice that of ofloxacin because the other enantiomer has no anti-bacterial activity (modified after Naber and Adam, 1998).

Chemotherapy (PEG). Those fluoroquinolones that are most often used today for the treatment of bacterial infections, such as urinary tract infections or respiratory tract infections, and that are considered relatively safe and well-tolerated drugs are compiled in Table 1, according to the PEG classification (Naber and Adam, 1998). In addition, a list of 12 quinolones is presented which were stopped during development, taken from the market or are used only very restrictively due to their specific toxicities (Table 2).

With the drugs used most often (Table 1), the overall rate of adverse reactions was very similar for the quinolone and the comparator in most clinical trials. However, therapy with fluoroquinolones is associated with several hazards and risks that must be considered and weighed against possible benefits of a quinolone therapy before a compound of this class can be prescribed. Three drugs had to be taken from the market in the 1990s due to rare, but serious toxicities.

2. Severe quinolone toxicities leading to market withdrawal

In 1992, it was noticed that the use of *temafloxacin* was associated with a syndrome of hemolysis, renal failure, and thrombocytopenia. The estimated incidence of the syndrome was 1/5000 prescriptions—an incidence too low to be detected reliably during clinical studies before marketing. Due to this toxicity, the drug was withdrawn from the market shortly after approval for clinical use. A similar pattern of adverse ef-

Table 2
Twelve fluoroquinolones which are no longer used or have limited significance due to their specific toxicities

Fluoroquinolone	Year [a]	Major reason for limited significance or withdrawal
Enoxacin	1985	Inhibition of cytochrome p450
Pefloxacin	1985	Tendopathies, phototoxicity, etc.
Fleroxacin	1990	Phototoxicity, CNS effects
Sitafloxacin	1991	Phototoxicity
Temafloxacin [b]	1992	Hemolytic uremic syndrome
Lomefloxacin	1993	Phototoxicity
BAYγ3118 [b]	1993	Phototoxicity
Sparfloxacin	1994	Phototoxicity, QT prolongation
Tosufloxacin	1996	Thrombocytopenia, nephritis
Trovafloxacin [b]	1999	Hepatotoxicity, CNS effects (e.g. lightheadedness)
Grepafloxacin [b]	1999	QT prolongation, arrhythmia, nausea
Clinafloxacin [b]	1999	Phototoxicity, hypoglycemia, inhibition of cytochrome P450

[a] Year of launch or year of decision (stop of development or market withdrawal) as far as known.
[b] Development discontinued or taken off the market shortly after launch.

fects has not been observed with the other fluoroquinolones. The mechanism of this side-effect is unknown.

The use of *trovafloxacin* was associated with severe hepatic reactions in rare cases. A total of 140 patients with severe hepatic reactions came to light after the drug had been prescribed worldwide approximately 2.5 million times. The hepatotoxic potential of trovafloxacin had been observed before in dogs. In these experiments elevated liver enzyme levels, which correlated with centrilobular, hepatocellular vacuolar degeneration, and necrosis were observed at doses exceeding therapeutic doses. However, because the effect was reversible and no serious hepatotoxicity occurred during clinical trials in several thousand patients, the hepatotoxic effects observed in animals were not considered relevant for patients treated with therapeutic doses.

The situation was similar for *grepafloxacin*. From the toxicological studies performed during preclinical development, it was known that the potential of the drug to induce cardiac arrhythmia was higher than that of the other quinolones (e.g. ciprofloxacin). However, since the effect on the QT-interval in humans after oral administration was small and based on the favorable experience during clinical investigation, it was considered to be without risk for humans. After its launch, a few cases of severe cardiac events were reported in association with the therapeutic use of grepafloxacin, and, although such events had been reported very rarely, it was withdrawn in all countries.

Taken together, there is probably no other class of drugs used widely that has generated three compounds exhibiting different kinds of toxicity that were withdrawn from the market shortly after their introduction. Furthermore, the clinical development of another fluoroquinolone, clinafloxacin, was stopped shortly before the anticipated launch. In this case, a pronounced phototoxic potential was at least one of the reasons for this decision. For a more detailed description of the fluoroquinolone-induced toxicities the reader is referred to a comprehensive review published recently (Stahlmann and Lode, 2000).

Table 3
Incidence of adverse events during clinical trials of levofloxacin, moxifloxacin and gatifloxacin (causal relationship not always clarified)

Event	Incidence (% of patients)
Gastrointestinal tract	
Nausea	7.1–8
Diarrhea	4–5.9
Vomiting	1.7–2.2
Abdominal pain	2–2.6
Dyspepsia	1.4–2.5
Central nervous system	
Dizziness	2.9–3
Headache	2–6.4
Insomnia	<1–4

Modified after Breen et al. (1999), Ortho-McNeil (1999) and Springsklee et al. (2000).

3. Common side-effects of quinolones

Nausea, vomiting, diarrhea and other reactions of the *gastrointestinal tract* are among the most often registered side-effects during therapy with quinolones. Compared to other groups of antibacterial agents with a broad spectrum (e.g. penicillins or cephalosporins) incidences of diarrhea are rather low. Diarrhea was noticed during clinical trials with the newer quinolones such as levofloxacin, moxifloxacin and gatifloxacin at approximately 4–6%. Some of the gastrointestinal reactions, such as nausea and vomiting, could also be signs of the neurotoxic effects of quinolones. Nausea was the most common adverse event during preregistration clinical trials and occurred at a frequency of approximately 8% of the patients who were treated with levofloxacin, moxifloxacin or gatifloxacin; incidence of vomiting was 2% (Table 3). Although clinical trials today are conducted according to standardized guidelines, a direct comparison of the incidences of adverse events as observed during the clinical trials with specific compounds should not be performed. Therefore, in Table 3 data for the individual quinolones are not presented separately, but rather as a range of the incidences. Obviously, no major differences exist between these drugs, as the ranges are narrow.

For a rational evaluation of quinolone *neurotoxicity*, it is important to distinguish mild reactions of the central nervous system (CNS) from severe reactions that require interruption of therapy. Mild reactions may occur in the form of headache, dizziness, tiredness, or sleeplessness. Furthermore, abnormal vision, restlessness, bad dreams, etc. have been reported in some instances. Severe neurotoxic side-effects are rare ($< 0.5\%$), but psychotic reactions, hallucinations, depressions, and grand mal convulsions have been noticed during therapy with most quinolones developed so far, and the possibility for such effects must be considered when a patient is treated with these drugs.

The dose dependency of the CNS effects of a quinolone became obvious in an early double-blind evaluation of fleroxacin, using 400, 600 and 800 mg once daily for 7 days for the treatment of uncomplicated genital infections. *Severe insomnia* was registered in 8% of the patients treated with 400 mg daily, but in approximately 60% of the patients (16/26) receiving the once daily 800 mg regimen, which is not licensed or recommended for therapy (Bowie et al., 1989).

Pathogenesis of the *neurotoxic effects* of fluoroquinolones is still unknown. The GABA antagonistic effects of quinolones in vitro depend on their substituent in position 7 of the heterocyclus. Those derivatives with a free piperazinyl group show stronger activities in such assays than quinolones with a methylated piperazine ring. However, the effects of quinolones on binding of ^{3}H-GABA or ^{3}H-muscimol (a GABA receptor agonist) to its receptor are weak and cannot explain their epileptogenic properties (Akahane et al., 1989; Takayama et al., 1995).

The hippocampus slice model has also been used for studying the neurotoxic effects of a series of fluoroquinolones. The determination of the field potentials in the CA1 region of the rat hippocampus slice allowed the assessment of the excitatory potential of fluoroquinolones. All compounds increased the population spike amplitude in a concentration-dependent manner. Ofloxacin, ciprofloxacin and moxifloxacin were among those that increased the population spike amplitude only moderately, whereas trovafloxacin, clinafloxacin and some investigational compounds were much more excitatory (Schmuck et al., 1998).

All quinolones form chelate complexes with di- and trivalent cations (Kawai et al., 1996). Therefore, it is of interest that in this in vitro system, slight changes in magnesium concentrations led to a strong amplification of the effects. For example, clinafloxacin (2 μmol/l) induced an increase in the population spike amplitude of more than 200% at the physiological Mg^{2+} concentrations of 2 mmol/l. A slight decrease in Mg^{2+} concentrations (1.75 mmol/l) potentiated the clinafloxacin effect very strongly. It was shown that MK 801, a selective channel blocker of the NMDA receptor, abolishes the excitatory effects of the quinolone clinafloxacin, suggesting the involvement of the NMDA channel in its effects in the hippocampus slice model. MK 801 has also been reported to antagonize the proconvulsive action of fluoroquinolones in mice. It is of further interest that seizures induced by *magnesium deficiency* can be antagonized by MK-801. Considering the Mg^{2+} chelating properties of fluoroquinolones, it is tempting to speculate that the excitatory potency of fluoroquinolones might be based on the activation of the NMDA receptor by abolishing the Mg^{2+} block in the ion channel (Schmuck et al., 1998).

4. Effects on the cardiovascular system

The above-mentioned withdrawal of grepafloxacin shows that severe cardiovascular toxicity can be induced by some quinolones. Animal experiments as well as clinical experience show that the cardiotoxic potentials of sparfloxacin and grepafloxacin are considerably higher than those of the other fluoroquinolones: they have the potential to induce *torsade de pointes*, a polymorphic ventricular tachycardia linked to pronounced QT-interval prolongation. A common structural feature of these two quinolones is a substituent in position 5 of the molecules: a methyl group in grepafloxacin and an amino group in sparfloxacin. Possibly, this structural similarity provides an explanation for the higher

potential for cardiotoxicity of these quinolones. Less pronounced prolongation of the QT interval has also been observed with the other fluoroquinolones.

Recently, data have been published on the effects of quinolones on the human cardiac potassium channel HERG, which is of interest, because it is known that the drug-induced blockade of this channel often provides a mechanistic explanation for QT-interval prolongation and arrhythmias. Results indicate that major differences exist for individual quinolones: sparfloxacin and grepafloxacin inhibit the channel at concentrations of 18 and 50 μmol (IC_{50}); IC_{50} values of moxifloxacin and gatifloxacin were 129 and 130 μmol, whereas the corresponding concentrations of ciprofloxacin, levofloxacin or ofloxacin are > 900 μmol (Anderson et al., 2001; Kang et al., 2001).

During the clinical development of moxifloxacin an extensive ECG testing programme was conducted in phase III trials. The 'normal' QT interval is 450 and 470 ms in males and females, respectively, but the physiological intraindividual variability is considerable (15–70 ms). The CPMP has defined criteria for 'significant' QTc prolongations; these include: (1) any QT interval > 500 ms; (2) any QT interval changes of > 60 ms; (3) QT prolongation of > 30 ms above the normal value; or (4) changes of > 15%. In 2.8% of the 787 patients, such 'significant' QT prolongations were noticed. Therefore, the drug should be avoided in patients with known prolongation of the QT interval, patients with uncorrected hypokalemia or hypomagnesemia and patients receiving class IA (e.g. quinidine, procainamide) or class III (e.g. amiodarone, sotalol) anti-arrhythmic agents. Corresponding restrictions are provided for gatifloxacin.

Although the potential for the HERG channel blockade differs among the individual quinolones, it seems prudent as a general rule to use quinolones restrictively in patients with underlying severe cardiac disease or electrolyte disturbances.

5. Phototoxicity, photocarcinogenicity

With respect to *phototoxicity* major differences exist between the quinolones and the structure–toxicity relationships are well known. Photoreactivity and thus phototoxicity is strongly influenced by the substituent in position 8. Drugs that are substituted with an additional chlorine or fluorine atom in this position, such as clinafloxacin, fleroxacin, lomefloxacin or sparfloxacin, generally exhibit a relatively high phototoxic potential, but quinolones with a methoxy substituent at position 8, as present in the molecules of moxifloxacin or gatifloxacin, exhibit significantly increased stability to UV light; they are not phototoxic under therapeutic conditions. Phototoxic quinolones induce the formation of singlet oxygen and radicals that cause severe tissue damage.

Some of the quinolones with pronounced photoinstability have been shown to be photomutagenic and photocarcinogenic. In a long-term phototoxicity study in Skh-1 mice, quinolones such as fleroxacin, ciprofloxacin, lomefloxacin, ofloxacin or nalidixic acid caused skin tumors. Differences in latency period and in incidences of tumors were seen. Except for lomefloxacin, almost all the skin tumors were of the benign type. The meaning for patients treated with these drugs remains unclear, but a consequent prevention of exposure to sunlight or artificial UVA sources during treatment with phototoxic quinolones is strongly recommended, and derivatives with a high phototoxic potential should not be used, because less toxic alternatives are available.

6. Effects on connective tissue structures

6.1. Chondrotoxicity

Chondrotoxicity of quinolones, as observed in immature animals, can affect articular cartilage and the epiphyseal growth plate in dependence on the developmental stage. On the other hand, as the frequency of infections by multi-resistent pneumococci or other bacteria has increased rapidly in some countries during the last decade, obviously a need for the use of quinolones in

selected pediatric indications exists. For example, their use in childhood bacterial CNS and respiratory infections has been specifically requested (Schaad, 2000). Favorable clinical experience exists with the use of ciprofloxacin in juvenile cystic fibrosis patients (Hampel et al., 1997). It should be kept in mind, however, that although 'chondrotoxicity' is considered a 'class effect', major differences seem to exist with respect to the risks associated with individual quinolones and the experiences with ciprofloxacin cannot be regarded as indicative for the whole group of fluoroquinolones. Ciprofloxacin has a limited bioavailability and a short half-life leading to a comparatively low systemic exposure (low AUC). Pefloxacin, which leads to 5–10 times higher systemic exposure, has been described to be associated with arthropathy in humans at high incidences (Pertuiset et al., 1989). Thus, for pharmacokinetic—and probably owing to other unknown reasons—it is not justified to generalize the clinical results with *one* quinolone in pediatrics to the whole class of compounds (Stahlmann and Lode, 1998).

BMS-284756 (= gerenoxacin) is a des-(6)-fluoroquinolone with anti-pneumococcal activity exhibiting a comparatively low chondrotoxic potential in juvenile dogs and has therefore been suggested as a possible candidate for pediatric indications (Kawamura et al., 2000). In routine toxicological studies, treatment of 6-week-old rats with BMS-284756 at daily doses of 400 mg/kg or greater for one or three months induced erosions, blisters and chondrocyte degeneration in joint cartilage, but in 4-week-old rats treated with doses up to 600 mg BMS-284756/kg body weight, toxic effects on the knee joint cartilage have not been observed. In a direct comparative toxicological experiment, ciprofloxacin did not have any effect on the joint cartilage either, but ofloxacin induced typical cartilage lesions (Table 4). If this model is predictive for human risk, then BMS-284756 and ciprofloxacin should be more suitable for pediatric use than ofloxacin (Kappel et al., 2001).

Pathogenesis of chondrotoxicity can probably be explained by the magnesium-chelating properties of these drugs, leading to radical formation and finally to irreversible cartilage lesions. Early data from the 1950s showed that in juvenile dogs fed on magnesium-deficient diet, gait alterations that closely resemble those observed after quinolone treatment were described. In rats, joint cartilage lesions observed after feeding on a magnesium-deficient diet for 9 days or longer, could not be distinguished from lesions induced by quinolones (Stahlmann et al., 1995). The link of the chelating activity of quinolones to their chondrotoxicity is further substantiated by the fact that quinolone-induced cartilage lesions can be diminished by the supplementation of magnesium and/or tocopherol (Stahlmann et al., 1999).

6.2. Tendopathies

Another manifestation of toxic effects of quinolones on connective tissue structures are *tendopathies*. Almost two decades ago Bailey et al. (1983) first described two patients after renal transplantation who developed tendinitis during treatment with norfloxacin. In 1991, the first cases of fluoroquinolone-associated tendon ruptures

Table 4
Chondrotoxicity of garenoxacin (= BMS-284756) and other quinolones in juvenile animals

Quinolone	Dose (mg/kg)	Effect
I. Rat (4 weeks old, n = 7–16 per group)		
Garenoxacin	600	0
Ciprofloxacin	600	0
Ofloxacin	600	++
II. Beagle dog (3 months old, n = 3 per group)		
Garenoxacin	30 [a]	0
	50	+
	60 [a]	+
Norfloxacin	30 [a]	+
	50	+
	60 [a]	++
Ciprofloxacin	30 [a]	+
	50	+

0 = dog: no blister formation; rat: no histological alterations; + = dog: blisters present in cartilage, but not in all joints investigated, or only slightly expressed. ++ = dog: blisters present in cartilage of all joints investigated; rat: histologically demonstrable defects in knee joint cartilage (modified after Kawamura et al., 2000; Kappel et al., 2001).

[a] Intravenous administration, the animals of the other groups were treated orally.

were reported; nearly 1000 cases of fluoroquinolone-induced tendinitis had been reported to the French drug surveillance agency until 1997. Fewer cases have been reported in other countries. Pefloxacin is the fluoroquinolone that is most often associated with cases of tendinitis; the fact that this drug is mainly marketed in France could explain some of the geographic disparities, but underreporting seems to be a more important aspect. In a compilation of more than 400 cases, treatment with ofloxacin, norfloxacin and ciprofloxacin also, besides pefloxacin, were associated with tendinitis and tendon ruptures. Of major concern is the fact that Achilles tendon ruptures were described to occur for as long as 120 days after start of treatment and can occur even after withdrawal of the drug (Pierfitte and Royer, 1996).

Publications from the Netherlands and other European countries underline the French experience. In the first extensive retrospective study in approximately 11 000 patients treated with antibiotics, four cases of tendinitis were identified in 418 patients treated with ofloxacin indicating that the risk for tendon disorders might be higher than assumed so far (Van der Linden et al., 1999). The authors also provide detailed information on 42 spontaneous reports of fluoroquinolone-associated tendon disorders, including ten patients with tendon rupture. Sixteen cases were attributed to ofloxacin, thirteen to ciprofloxacin, eight to norfloxacin, and five to pefloxacin. There was a male predominance, and the median age of the patients was 68 years. Most of the reports concerned the Achilles tendon and 57% of the patients had bilateral tendinitis. The latency period between the start of treatment and the appearance of the first symptoms ranged from 1 to 150 days with a median of 6 days. Again, ofloxacin was implicated most frequently relative to the number of filled prescriptions in the Netherlands (Van der Linden et al., 2001).

In addition to the clinical experience a number of toxicological studies has been published confirming that the quinolone-induced tendopathy is a drug-induced, dose-dependent toxic effect of these agents. Kato et al. (1995) described edema with mononuclear cell infiltration in the inner sheath of the Achilles tendon after single oral administration of pefloxacin or ofloxacin. The tendon lesions were induced in juvenile rats (4 weeks of age) but not in 12-week-old rats. Tendon lesions were inhibited by co-administration with dexamethasone and *N*-nitro-L-arginine methyl ester. Phenidone (1-phenyl-3-pyrazolidinone) and 2-(12-hydroxydodeca-5,10-diynyl)3,5,6-trimethyl-1,4-benzoquinone (AA861) also decreased the incidence of tendon lesions. In contrast, catalase, dimethyl sulfoxide, indomethacin, pyrilamine, and cimetidine did not modify these tendon lesions. These results suggest that nitric oxide and 5-lipoxigenase products partly mediate fluoroquinolone-induced tendon lesions (Kashida and Kato, 1997).

A group of French toxicologists investigated the effect of pefloxacin on Achilles tendon proteoglycans and collagen in rodents and showed convincingly that quinolone-induced oxidative stress on the Achilles tendon altered proteoglycan anabolism and oxidized collagen. Biphasic changes in proteoglycan synthesis were observed after a single administration of pefloxacin, consisting of an early inhibition followed by a repair-like phase. Pefloxacin treatment for several days induced oxidative damage of collagen type I, with the alterations being identical to those observed in the experimental tendinous ischemia and reperfusion model. Oxidative damage was prevented by the co-administration of *N*-acetylcysteine (Simonin et al., 2000).

Recent experiments from our group have shown that ultrastructural alterations in tenocytes can be observed in juvenile and adult rats after treatment with quinolones. Effects were more pronounced when the animals were simultaneously given a magnesium-deficient diet, suggesting that the pathophysiology of tendopathy resembles that of arthropathy (Shakibaei et al., 2000). When we studied the Achilles tendons from quinolone-treated adult rats by electron microscopy 4–12 weeks after treatment with single oral doses of ofloxacin, levofloxacin or fleroxacin, we were able to detect specific, pathological alterations already at the lowest dose level (30 mg/kg), which increased in severity with increasing doses. Tenocytes detached from the extracellular matrix and exhibited degenerative changes such as multiple

vacuoles and large vesicles in the cytoplasm that resulted from swelling and dilatation of cell organelles (mitochondria, endoplasmic reticulum). Other findings were a general decrease of the fibril diameter and an increase in the distance between the collagenous fibrils (Shakibaei and Stahlmann, 2001; Shakibaei et al., 2001a).

By Western blot analysis, we studied the effects of ciprofloxacin or a magnesium-deficient diet on cellular or matrix proteins of Achilles tendons in immature dogs. Densitometric analysis of the immunoblots with anti-collagen type I, anti-elastin, anti-fibronectin, and anti-integrin antibodies showed a significant reduction of all proteins isolated from the tendons with a buffer that extracted a soluble protein fraction. Results were similar for the ciprofloxacin treated dogs as well as the magnesium-deficient dogs. These findings support our hypothesis that quinolone-induced toxic effects on connective tissue structures are due to the magnesium-antagonistic effects of these anti-bacterial agents. They also indicate that patients with a latent magnesium deficiency could be at an increased risk of quinolone-induced tendon disorders (Shakibaei et al., 2001b).

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